ACTA RADIOLOGICA

FOUNDED IN 1921 BY GÖSTA FORSSELL

OFFICIAL ORGAN OF THE RADIOLOGICAL SOCIETIES OF DENMARK FINLAND NORWAY AND SWEDEN

THERAPY PHYSICS BIOLOGY

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INDICES to Vol. 15 (1976)

February April June August October December

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ABSTRACTS

TVETEN L *Spinal cord vascularity I Extraspinal sources of spinal cord arteries in man* Acta radiol Diagnosis 17 (1976) 1

The arrangement of extraspinal sources of the spinal cord arterial supply in man is more complicated than previously described especially with regard to the origin and branching of the aortic segmental arteries The fact that other arteries in the neck than the vertebral artery such as the costocervical trunk and the ascending cervical artery may contribute to the supply of the cervical cord is confirmed and also the occurrence of two or more spinal branches from different sources entering the same intervertebral foramen Frequent occurrence of two or more segmental arteries arising from a common stem and variations in the branching of the subcostal arteries were found their functional significance on the spinal cord circulation is not known The fact that no significant anterior root artery was ever seen at the level of the vascular anomaly suggests that the anomaly is of no clinical importance Nevertheless obstruction of a common stem may entail the risk of spinal cord infarction due to involvement of an important posterior root artery On the other hand the spinal cord seems to be fairly well protected against ischaemic injury following limited interference with the extraspinal arteries due to a profuse supply of intra and extraspinal collaterals

UDEN R Secretin and epinephrine combined in celiac angiography Acta radiol Diagnosis 17 (1976) 17

Celiac angiography was performed in 39 patients without pharmaceuticals with epinephrine or secretion alone and with secretin and epinephrine combined With secretin and especially with secretin together with epinephrine the visibility of pancreatic arteries, capillaries and veins increased with a consequent improvement in information Normal small veins such as the choledochal and the pancreaticoduodenal veins have proved to be of great diagnostic value With secretin and epinephrine combined abnormal veins and nearly always abnormal capillaries became contrast filled in malignancy of the pancreas

PINET A TRAN MINH V BOUCHERAT M DUBREUIL A and MAGIS J P Hepatography with intravenously injected emulsified iodolipids Preliminary results Acta radiol Diagnosis 17 (1976) 41

Hepatography by slow intravenous infusion of AG 60 99 Guerbet (iodized lipids in a stable *emulsion) was performed in 31 patients aged 17 to 77 years to detect* circumscribed hepatic lesions metastases cysts and hepatic abscesses The tolerance was good with minor side effects unrelated

present for exploration of the liver

LAVAL JEANTET M LAMARQUE J L DREUX P LAVAL JEANTET A M and LAUNAY J Hepatosplenography by intravenous injection of a new iodized oily emulsion Acta radiol Diagnosis 17 (1976) 49

Hepatosplenography with intravenously injected iodized lipid emulsion has been performed in 30

JENSEN J TH and KLINGE T Hemangioma of the liver Report of two cases Acta radiol Diagnosis 17 (1976), 61

Two cases of hepatic hemangiomas are described, diagnosed by angiography and controlled by repeat angiography after 2 5 and 6 years, respectively The radiologic appearance is described and although it varies, angiography must be considered the safest method of diagnosis biopsy is contraindicated Steroid therapy seems to be a possible mode of treatment

TRAGÅRDH B, LYNCH P and TRAGÅRDH M Coronary angiography with diatrizoate and metrizamide Comparison of ionic and non ionic contrast medium effect on coronary blood flow in dogs *Acta radiol Diagnosis 17 (1976), 69*

The non ionic contrast medium metrizamide produced a smaller coronary flow increase than the ionic medium diatrizoate after injection into the main left coronary artery in dogs and had also a *shorter transit time through the coronary vessels* The coronary veins were better filled with metrizamide The reduced coronary flow effects of metrizamide compared to ionic contrast medium and the improved venous filling makes metrizamide a favorable contrast material for use in coronary angiography

LEVITAN H and RAPOPORT S Contrast media Quantitative criteria for designing compounds with low toxicity Acta radiol Diagnosis 17 (1976), 81

Toxicity of contrast media that are ionized iodobenzoic acids or their derivatives is highly correlated with lipid solubility, as measured by the octanol/water partition coefficient New contrast media have been designed with lower lipid solubility than media in current use, taking into account the *additive-constitutive nature of the partition coefficient of an organic compound If these contrast* media are chemically stable, they should also be less toxic It remains to be tested whether the relation between clinical toxicity and lipid solubility applies to nonionized contrast media as well

BJORK L Effect of epinephrine on the contractions in the normal renal pelvis in man A cineradiographic investigation Acta radiol Diagnosis 17 (1976), 93

In 22 normal subjects a marked increase in the frequency and degree of contractions of the renal pelvis occurred after injections of 6 to 10 μg of epinephrine into the renal artery Such injections may be used to increase the diagnostic value of cineradiography of the renal pelvis

SVAHN T and SPANGEN L Peritoneography in Spigelian hernias Acta radiol Diagnosis 17 (1976), 97

Twelve patients with a minor Spigelian hernia not involving the intestines have been examined by combined peritoneography and herniography The particular pathology of this hernia does not lend itself to be detected by these procedures

HÅRDSTEDT CH RUNDELIUS B and WELANDER U Photographic subtraction II Technical aspects and method Acta radiol Diagnosis 17 (1976) 101

Technical aspects of photographic subtraction of original films in black and white and blue and white (Medichrome) under standard development conditions available in any roentgen unit are described The adjustment necessary to control the γ value of the masking film takes advantage of the capacity of some graphic films to respond with different γ values on variation of the color of the exposure light

OLIN T., OLSSON T. H., SELVIK G. and WILLNER S. Kinematic analysis of experimentally provoked scoliosis in pigs with roentgen stereophotogrammetry. Acta radiol. Diagnosis 17 (1976), 107.

A three-dimensional method to analyse the kinematics of the spine has been applied to four pigs with experimentally provoked scoliosis. The advantages and limitations of the method are discussed and some interesting facts concerning the provoked curves are stressed.

JENSEN J TH and KLINGE T Hemangioma of the liver Report of two cases Acta radiol Diagnosis 17 (1976) 61

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PROGNOSTIC FACTORS IN MAMMARY CARCINOMA

A WALLGREN, C SILFVERSWÄRD and G EKLUND

An extensive literature exists on the prognostic value of various clinical and microscopic factors in carcinoma of the breast However, few reports deal with the simultaneous influence of multiple factors on the clinical course of the disease Many prognostic factors were defined and adapted for multivariate analysis in a previous report (WALLGREN & SILFVERSWÄRD 1975) Some of these factors have now been analysed with respect to their bearing on the outcome of 581 cases treated with radical mastectomy

Material and Methods

Clinical material In the period 1961 through 1963, 591 women younger than 70 years, who were admitted for treatment of unilateral, invasive carcinoma of the breast, underwent radical mastectomy without previous irradiation or hormone medication Ten patients, whose available microscopic slides on re-scrutiny showed pure colloid (mucous) carcinoma were excluded from the material, which thus comprised 581 radically mastectomized women All but 9 received postoperative irradiation The axillary, supraclavicular and ipsilateral parasternal lymph node regions were irradiated in 382 patients, the parasternal and supraclavicular fields

From Radiumhemmet (Director Prof J Einhorn) and the Institute of Tumour Pathology (Director Prof G Moberger) Karolinska Sjukhuset, S 104 01 Stockholm, and the Statistical Institution, University of Stockholm S-113 47 Stockholm, Sweden Submitted for publication 10 October 1975

Table 2

Microscopic primary tumour variables. n = No. of patients

Microscopic classification
1) Infiltrating lobular (n = 80) 2) medullary with lymphoid infiltration (n = 33) 3) ductal, cribriform or papillary (n = 51) 4) ductal, comedo type (n = 35) 5) ductal, no further specification (n = 387)

Necrosis
1) None (n = 286) 2) few small areas (n = 60) 3) moderate (n = 113) 4) massive, large confluent areas (n = 122)

Tubule formation
1) Regular (n = 47) 2) moderately regular or small areas with few tubules (n = 82) 3) poor tubule formation or generally few tubules (n = 346) 4) non-tubular carcinoma types (lobular or medullary) (n = 111)

Lymphoid infiltration
1) Occasional lymphatic or plasma cells, no focal areas (n = 210) 2) small, scattered foci or narrow circumscribing zone (n = 204) 3) numerous large foci or wide circumscribing zone (n = 121) 4) massive infiltration throughout tumour (n = 46)

Size of nuclei
1) Small (n = 83) 2) fairly small (n = 163) 3) fairly large (n = [illegible]) 4) large (n = 108)

Variability of size of nuclei
1) None (n = 52) 2) slight (n = 225) 3) moderate (n = [illegible]) 4) marked (n = [illegible])

Contour of nuclei
1) Even (n = 9[illegible]) 2) slightly uneven (n = 23[illegible]) 3) uneven (n = 16[illegible]) 4) irregular (n = 78)

Mitotic frequency
1) Few mitotic figures, no hyperchromatic nuclei (n = [illegible]) 2) occasional mitoses or small numbers of hyperchromatic nuclei (n = 224) 3) moderate frequency or large numbers of hyperchromatic nuclei (n = 196) 4) many mitotic figures (n = 102)

Nucleoli
1) Just discernible (n = 20[illegible]) 2) clearly discernible (n = 19[illegible]) 3) enlarged (n = 1[illegible]3) 4) prominent (n = 67)

After ten years 222 of the patients had distant metastases, 204 had died of their malignancy and 79 from unrelated causes. A primary contralateral malignant tumour had been found in 20 patients. The ten-year survival rate was 63 per cent and the ten-year [illegible] rate 6[illegible] per cent.

Microscopy. Sections or paraffin blocks were available from the primary tumour and the axillary lymph nodes in all cases. The surgical specimens had already been [illegible] in a number of laboratories. The sizes and the numbers of the blocks [illegible] from the primary tumours and also the number of excised lymph nodes [illegible] considerably. As part of the prognostic [illegible] new slides were prepared [illegible] were reviewed at the Institute of Tumour Pathology. The slides which were

Table 1

Variables denoting 'microscopic' stage of the tumours. n = No. of patients

Size of tumour (greatest dimension)
1) ≤1 cm (n = 33), 2) 1.1 to 2 cm (n = 250), 3) 2.1 to 5 cm (n = 220), 4) >5 cm (n = 37), 5) multiple tumours or insufficient data (n = 41)

Axillary node metastases
1) None (n = 296), 2) micrometastases ≤2 mm (n = 25), 3) one macrometastasis (n = 78), 4) 2 to 3 macrometastases (n = 112), 5) 4 or more macrometastases (n = 70)

Perinodal growth
1) No metastases (n = 296), 2) metastases without perinodal growth (n = 103), 3) metastases with possible perinodal growth (n = 40), 4) metastases with evident perinodal growth (n = 79), 5) metastases with massive perinodal growth (n = 63)

only were irradiated in 186 patients without lymph node metastases. Radiation therapy was confined to the axillary region in the 4 remaining cases.

Axillary irradiation consisted of 170 to 190 kV roentgen radiation (HVL approximately 1 mm Cu), a dose of 2 400 R being delivered in 6 fractions to one anterior and one posterior field. For parasternal irradiation a short distance ^{60}Co unit was used (Edsmyr & Walstam 1963) or a maximum absorbed dose of 4 000 rad was administered in 8 fractions over three weeks, using a 12 to 15 MeV electron beam. The supraclavicular region was included in the anterior axillary field or selectively irradiated in the same way as the parasternal region.

Surgical or radiologic castration was performed on 154 patients, most of whom had axillary lymph node metastases.

The patients were re-examined at regular intervals. After some years the follow-up was in some cases continued at other hospitals or by letters to the patients. Local recurrences and distant metastases were treated with conventional methods, including hormonal procedures.

Patients who died without clinical or autopsy evidence of distant metastases were regarded as dead from unrelated causes. However, all deaths within a year of the primary treatment or of treatment for local recurrence were classified as malignancy deaths, as were all those that occurred after distant metastases had been detected. There were no deaths in the immediate postoperative period. A contralateral breast malignancy was regarded as a new primary tumour if there were no signs of distant metastases or of spread of tumour over the midline of the chest wall, in accordance with the clinical rules outlined by Haagensen (1971).

Five years after the radical mastectomy distant mestastases had been found in 172 patients, 134 of whom had died of their malignancy. Fifteen other patients had died from unrelated causes. A primary tumour of the contralateral breast had appeared in 9 cases. The five-year survival rate was 76 per cent and the five-year cure rate 70 per cent.

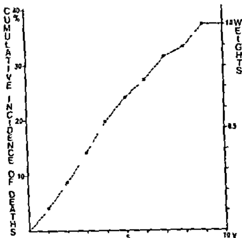


Fig. 1 Cumulative incidence of deaths from malignancy in 581 patients following radical mastectomy The weights were used to correct the survival rates for those who died from intercurrent causes or in whom a contralateral mammary carcinoma was detected during the period

based technique by which the original material is divided into mutually exclusive risk groups through a series of dichotomous splits Each split is made according to the explaining variable, predictor, that most reduces the variance of the dependent variable At each step it is easy to survey the alternative possibilities of splitting the clinical material

AID analysis was selected as a suitable method for a multivariate procedure, since the dependent variables were of dichotomous type (dead, alive) and because no assumption was necessary concerning a linear model The introduction of rules for terminating the partitioning process, based on calculation of the risk of artifact divisions (GAVATIN & EKLUND 1972, JEREB & EKLUND 1973, AVEN 1974) has reduced the danger of overestimating the explanatory value (EINHORN 1972) or of being misled by the vagaries of small numbers' (ARMITAGE & GEHAN 1974) In the present analysis the partitioning process was terminated when any further split would have produced a subgroup with less than 10 individuals or when the difference between subgroups did not reach the 0.05 significance level Significance was calculated as described by JEREB & EKLUND (1973) and by AVÉN (1974)

Microscopic classification and site of primary tumour, consisting of unordered, non numerical categories were free predictors, which implies that the order of the coded classes could be rearranged during the analysis All the other predictors were monotonic Predictors which comprised a number of observations with missing data and the predictor tubule formation containing the non-numerical category of non-tubular carcinoma types, were each transformed into two predictors in order to retain their character of monotonic variables (GAVATIN & EKLUND 1972)

The part of the variance of the dependent variable that could be ascribed to the most important split accomplished by each predictor was calculated This coefficient of determination, r^2, was converted to the corresponding correlation coefficient, r

Table 3

Clinical variables n = No of patients

Clinical stage (UICC 1968)
1) Stage I (n = 247) 2) stage II (n = 172), 3) stage III (n = 108), 4) insufficient data (n = 54)

Clinical assessment of tumour
1) *Greatest dimension ≤ 2 cm, T1 (n = 116), 2) greatest dimension 2 1 to 5 cm T2 (n = 324) 3)* greatest dimension > 5 cm, T3 (n = 86), 4) any size, direct skin or chest wall involvment, T4 (n = 13) 5) not palpable or multiple tumours, insufficient data (n = 42)

Clinical assessment of lymph nodes
1) None palpable, N0 (n = 297), 2) palpable, considered not malignant, N1a (n = 66) 3) palpable movable, considered malignant, N1b (n = 158), 4) fixed nodes, N2 (n = 22), 5) insufficient data (n = 38)

Site of primary tumour
1) Lateral (n = 258), 2) central (n = 173), 3) medial (n = 133) 4) insufficient data (n = 17)

Duration of signs and symptoms
1) < 1 month (n = 176) 2) 1 to 3 months (n = 138), 3) 3 to 6 months (n = 62) 4) > 6 months (n = 186) 5) insufficient data (n = 19)

Age of patient
1) < 45 years (n = 105), 2) 45 to 54 years (n = 211), 3) 55 to 69 years (n = 265)

stained by the van Gieson or haematoxylin-eosin methods, were mainly used in this investigation If available slides were substandard, new sections were prepared

The slides were examined without knowledge of the clinical course in the case The lymph node sections were not examined at the same time as the sections from the primary tumours

The microscopic variables were grouped as those pertaining to the extent of the malignant process—the 'microscopic' stage (Table 1) and features of the primary 'microscopic' stage (Table 1) and features of the primary tumour (Table 2) The *definitions largely agree with those in the previous investigation* (WALLGREN & SILFVERSWARD) The clinical variables are presented in Table 3

Statistical methods The analyses were performed with five- and ten-year survival as dependent variables For calculation of survival rates weights were allotted The weighting for a patient, who died of unrelated causes or in whom a new malignant tumour was detected in the contralateral breast during the *a*th year of follow-up, was the calculated risk of dying of malignancy within *a* − 0 5 years in relation to the total risk of death from malignancy during the whole follow-up period, i e 5 or 10 years The cumulative incidence (risk) is illustrated in Fig 1 The weighted number of patients (patients at risk) was used in all the calculations

Automatic interaction detector (AID) analysis was described by SONQUIST & MORGAN (1964) and was further elaborated by SONQUIST et coll (1971) It is a computer-

Table 5

Groups of factors indicating favourable prognosis AID analysis with five year survival as dependent variable

Characteristics	No of patients	Survival (per cent)
No metastases or metastases but no perinodal growth and few or occasional mitoses (Fig 4)	203	94
No metastases and tumour size less than 2 cm	177	94
Markedly or moderately regular tubule formation	124	95
(Plus massive or moderate elastosis, Fig 2)	65	100
Metastases with possible or evident perinodal growth and moderate or massive elastosis (Fig 4)	47	89
Clinical assessment T1 and N0 or N1a	104	94
Patients belonging to at least one of these groups	370	90

Table 6

Percentage of variance of survival attributable to sets of predictors

Set of predictors	AID analysis of survival	
	5 years	10 years
Clinical variables	9	6
Variables denoting microscopic stage	15	17
Microscopic features of primary tumour	10	9
All predictors	21	21

ten-year survival among patients who were still alive after 5 years (Table 4) A group with favourable five year survival, 94 per cent, was identified through the AID analysis (Table 5), viz 104 patients with tumours less than 2 cm (T1) and possibly without malignant lymph nodes (N0 or N1a) Their ten-year survival rate was 77 per cent The lowest survival rates were found for 61 patients in stage III with lymph nodes considered to be involved (N1b or N2) Their five- and ten-year survival rates were 46 and 35 per cent The variance of the dependent variable attributable to the clinical predictors was 9 per cent for five-year and 6 per cent for ten-year survival (Table 6)

Microscopic stage predictors (1) Size of tumour, (2) axillary node metastases and (3) perinodal growth were all significantly correlated with five- and ten year survival (Table 4) These predictors accounted for more of the variance of both five- and ten-year survival (R^2 = 15 and 17 per cent) than did the other predictor groups (Table 6)

Table 4

Correlation between predictors and survival In the calculation of coefficients it was assumed that each predictor consisted of two classes formed by the most important split of the material in regard to that predictor The levels of significance are indicated (p<0 05, ** p<0 01, *** p<0 001, N S p>0 05) F = free predictor*

Predictor	Correlation with survival r		
	0–10 years	0–5 years	5–10 years
Clinical variables			
Stage	−0 18***	−0 21***	N S
Assessment of lymph nodes	−0 18***	−0 22***	N S
Assessment of tumour	−0 17***	−0 20***	N S
Site of primary tumour (F)	0 10*	0 11*	N S
Age of patient	0 10*	−0 09*	N S
Duration of signs and symptoms	N S	N S	N S
Variables denoting microscopic stage			
Axillary node metastases	−0 30***	−0 31***	0 13**
Perinodal growth	0 28***	−0 33***	N S
Size of tumour	−0 28***	0 24***	−0 18***
Primary tumour variables			
Tubule formation	0 25***	0 23***	0 22***
Mitotic frequency	−0 23***	0 22***	−0 14**
Variability of size of nuclei	−0 19***	0 21***	N S
Elastosis	+0 16***	0 23***	N S
Nucleoli	0 16***	0 13**	0 10*
Microscopic classification (F)	0 14**	0 13**	0 11*
Contour of nuclei	0 13**	−0 19***	N S
Size of nuclei	0 10*	−0 12**	N S
Lymphoid infiltration	N S	0 09*	N S

The advantage of r over r^2 is that the direction of the correlation is indicated The coefficients of determination for the total AID analyses, R^2, were also calculated

Results

The correlation coefficients between the predictors and the dependent variables, viz the five- and ten-year survival for all the 581 patients and the ten-year survival in the 423 who survived for at least 5 years, appear in Table 4

Clinical predictors Significant correlations with five- and ten-year survival were found for (1) clinical stage, (2) clinical assessment of lymph nodes and (3) clinical assessment of tumour (Table 4) None of the clinical variables was correlated with the

Table 5

Groups of factors indicating favourable prognosis AID analysis with five-year survival as dependent variable

Characteristics	No of patients	Survival (per cent)
No metastases or metastases but no perinodal growth and few or occasional mitoses (Fig 4)	203	94
No metastases and tumour size less than 2 cm	177	94
Markedly or moderately regular tubule formation	124	95
(Plus massive or moderate elastosis, Fig 2)	65	100
Metastases with possible or evident perinodal growth and moderate or massive elastosis (Fig 4)	47	89
Clinical assessment T1 and N0 or N1a	104	94
Patients belonging to at least one of these groups	370	90

Table 6

Percentage of variance of survival attributable to sets of predictors

Set of predictors	AID analysis of survival	
	5 years	10 years
Clinical variables	9	6
Variables denoting microscopic stage	15	17
Microscopic features of primary tumour	10	9
All predictors	21	21

ten year survival among patients who were still alive after 5 years (Table 4) A group with favourable five-year survival, 94 per cent, was identified through the AID analysis (Table 5), viz 104 patients with tumours less than 2 cm (T1) and possibly without malignant lymph nodes (N0 or N1a) Their ten-year survival rate was 77 per cent The lowest survival rates were found for 61 patients in stage III with lymph nodes considered to be involved (N1b or N2) Their five- and ten-year survival rates were 46 and 35 per cent The variance of the dependent variable attributable to the clinical predictors was 9 per cent for five-year and 6 per cent for ten-year survival (Table 6)

Microscopic stage predictors (1) Size of tumour, (2) axillary node metastases and (3) perinodal growth were all significantly correlated with five- and ten-year survival (Table 4) These predictors accounted for more of the variance of both five- and ten-year survival (R^2 = 15 and 17 per cent) than did the other predictor groups (Table 6).

Table 7

Distribution of cases and survival according to some primary tumour predictors The most important split of the original material by each predictor is indicated by a dividing line

Predictor	Distribution (per cent)	Survival (per cent)	
		5 years	10 years
Microscopic classification			
Ductal cribriform or papillary	9	94	85
Infiltrating lobular	14	80	66
Medullary with lymphoid infiltration	6	78	75
Ductal no further specification	66	76	61
Ductal comedo type	6	54	43
Tubule formation			
Regular	7	95	90
Moderately regular	14	95	84
Poor	59	69	53
Non tubular carcinomas	19	79	68
Elastosis			
None	49	71	60
Small areas	10	55	45
Moderate	19	87	68
Massive	21	90	78
Mitotic frequency			
Few mitoses	10	98	95
Occasional mitoses	39	83	69
Moderate frequency	34	70	57
Many mitoses	18	62	44
Total		76	63

Correlation was also found between size of tumour and axillary node metastases and ten-year survival among patients who were still alive after 5 years

A group with 94 per cent five-year survival rate consisted of 177 patients without metastases and with tumours less than 2 cm in diameter (Table 5), their ten-year survival rate was 86 per cent The same ten-year survival rate was found in the AID analysis for 191 patients without metastases or with micrometastases and with tumours less than 2 cm A group with 49 per cent five-year survival rate was identified, viz 135 patients with two or more involved nodes and with possible, evident or massive perinodal growth Their ten-year survival rate was 32 per cent The lowest ten-year survival rate, 13 per cent, was found among 38 patients with two or more involved nodes, massive perinodal growth and whose tumours measured more than 2 cm or were multiple

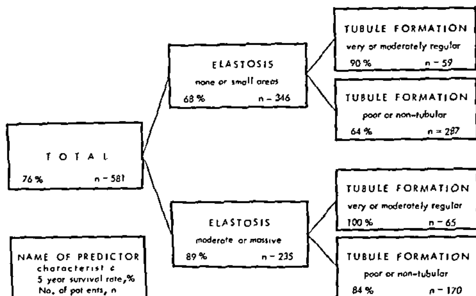


Fig 2 AID analysis of the prognostic importance of microscopic primary tumour predictors with five year survival as dependent variable

Microscopic primary tumour predictors Except for lymphoid infiltration all the predictors in this category correlated with both five- and ten year survival (Table 4) Survival in relation to (1) microscopic classification, (2) tubule formation, (3) elastosis and (4) mitotic frequency appears in Table 7 The result of the AID analysis of the prognostic significance of the microscopic primary tumour predictors when five-year survival was the dependent variable is surveyed in Fig 2

The predictor that accounted for most of the variance was elastosis, but significant partitions of the original material could have been obtained from tubule formation, mitotic frequency, variability of size of nuclei and contour of nuclei Moderately or very regular tubule formation was associated with high survival rates, and when this microscopic feature was combined with moderate or massive elastosis (65 patients) no deaths from malignancy (Fig 2, Table 5) had occurred The explanatory value R^2 was 10 per cent (Table 6) The analysis, however, did not identify any groups with very poor prognosis

When ten-year survival was the dependent variable (Fig 3), the material was first split according to tubule formation The predictors mitotic frequency, variability of size of nuclei, elastosis and nucleoli could also have given significant splits Two groups with favourable prognosis were thus identified In tumours with markedly or moderately regular tubule formation the ten year survival rate was 86 per cent, and when there was poor or no tubule formation with scanty mitoses the corresponding rate was 93 per cent (Fig 3) No group with very poor prognosis was identified R^2 was 9 per cent (Table 6)

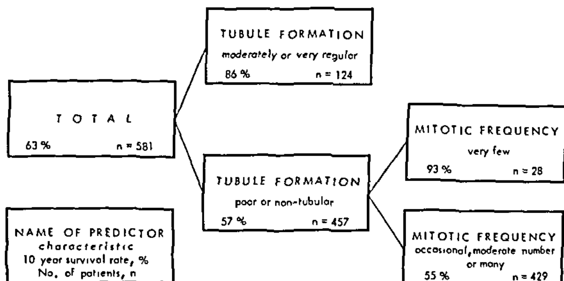


Fig 3 AID analysis of the prognostic importance of microscopic primary tumour predictors with ten year survival as dependent variable

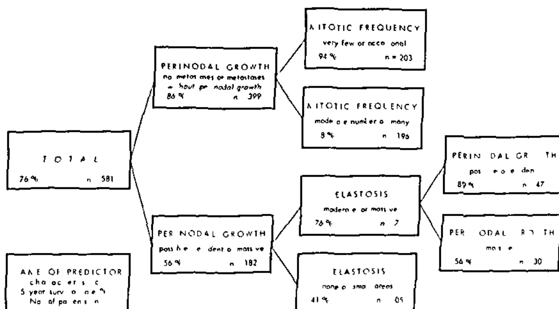


Fig 4 AID analysis of the prognostic importance of clinical and microscopic predictors with five-year survival as dependent variable

Tubule formation and mitotic frequency were related to ten-year survival in the patients who were *still alive after 5 years* (Table 4)

AID analyses with all predictors as explaining variables The most important partitioning of the original material with both five- and ten-year survival was obtained with the predictors that denoted extent of the disease in axillary lymph nodes

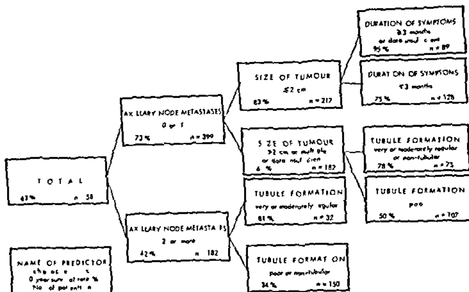


Fig 5 AID analysis of the prognostic importance of clinical and microscopic predictors with ten year survival as dependent variable

When five year survival was the dependent variable, perinodal growth was the major predictor It distinguished the cases without metastases, or with metastases but no perinodal growth, from those with metastases and possible, evident or massive perinodal growth (Fig 4) The AID analysis demonstrated two prognostically favourable groups (Fig 4 Table 5), viz. without metastases or with metastases but no perinodal growth and with very few or only occasional mitoses (five-year survival rate 94 per cent) and cases with possible or evident perinodal growth and moderate or massive elastosis (89 per cent five year survival) The poorest survival rate—41 per cent—was found in 105 cases with possible, evident or massive perinodal growth and no or minimal elastosis R^2 was 21 per cent (Table 6)

When ten year survival was substituted for five year, the material was first split with regard to axillary node metastases (Fig 5) Cases with 2 or more involved nodes were separated from cases without metastases or with only micrometastases or one macrometastasis A group with 95 per cent ten year survival consisted of 89 patients who had had symptoms or signs for more than three months and whose tumours at operation were less than 2 cm in diameter and had produced at most one macrometastasis in the axillary nodes By contrast, the ten year survival rate among 150 patients with two or more involved nodes from tumours with poor tubule formation or from non tubular carcinoma was only 34 per cent (Fig. 5) R^2 was 21 per cent (Table 6)

The analyses with five year survival as the dependent variable and with various

sets of predictors as explaining variables revealed several groups with high survival rates (Table 5) Of the 581 patients, 370 belonged to at least one of these groups and 90 per cent of them were still alive after 5 years and 78 per cent after 10 years In the 192 cases with features of at least two of the groups the corresponding rates were 98 and 88 per cent, respectively

AID analysis was further performed with ten-year survival as the dependent variable and including only those patients who had lived for at least 5 years Their ten-year survival rate was 83 per cent Few of the predictors were significantly correlated to that survival (Table 4) Only 7 per cent of the variance of survival could be accounted for

Discussion

Many single features of mammary carcinoma and combinations of a few of these have been demonstrated to influence the outcome, but few reports have appeared in which the prognostic value of multiple factors was simultaneously assessed ALDERSON et coll (1971) found from a multiple regression analysis of 15-year survival in patients with operable mammary carcinoma that axillary lymph node metastases, *the clinical stage and the size of the tumour were the most important variables* independently explaining survival Other major factors were radiation therapy, which negatively influenced survival, stromal reaction, grade of malignancy and year of treatment This last variable was positively correlated to survival, i e patients who were treated during the later years had higher survival rates than those treated in the earlier years

In order to minimize the time factor, the present analysis was limited to the period 1961 through 1963 Like ALDERSON et coll, it was found that the variables mainly involved in survival were those relating to the extent of the tumour (Table 4, Figs 4, 5) The prognostic influence of the number of involved axillary lymph nodes is well documented in the literature (FISHER & SLACK 1970, FISHER et coll 1975) Since the number of lymph node sections varied considerably within the case series, the estimated numbers of involved nodes probably were too low in some cases Such underestimation would presumably reduce the value of lymph node involvement as a predictor of prognosis

Perinodal extension of carcinoma has been shown to indicate poor prognosis (*HULTBORN & TÖRNBERG 1960*, MCDIVITT et coll 1968) In our AID analysis on five-year survival the first split distinguished the cases with possible, evident or massive perinodal growth from those without metastases, or with metastases but no perinodal growth (Fig 4) The advantage of this predictor over the number of involved nodes is that, whereas the latter may vary as a consequence of the quality of the gross examination of the surgical specimen, nodes with perinodal extension of carcinoma are most likely to be excised for examination (MCDIVITT et coll)

Tumour size is another factor of recognized prognostic significance (FISHER et

coll (1969) In the present material its explanatory value remained after the material had been split with respect to axillary node metastases (Fig 5)

Tubule formation and mitotic frequency were two important prognostic features of the primary tumours In contrast to the other microscopic primary tumour predictors, they also exerted a significant influence on the ten year survival of the patients who were alive after 5 years (Table 4) Together with 'irregularity of shape and staining of nuclei' they are included in the malignancy grading system evolved by SCARFF and BLOOM (SCARFF & TORLONI 1968) Nuclear irregularity was subdivided into the two predictors variability of size and of contour Both were significantly correlated with five-year survival but not with ten year survival of patients who where alive after 5 years

Moderate or massive elastosis was found to imply a high five-year survival rate This is consistent with the finding by SHIVAS & DOUGLAS (1972) of a longer mean survival time in patients who died of mammary tumour when there was gross elastosis In contrast to FISHER et coll (1975), who used slides specifically stained for elastica, diffuse elastosis was not included in the present microscopic grading Focal areas of elastosis were easily demonstrable in sections stained with van Gieson or haematoxylin-eosin Elastosis was seen mainly around ducts, but was sometimes visible in the stroma of the tumour Though in the present investigation elastosis was important as a predictor of five year survival, it was not significantly correlated with the ten year survival in patients who had lived for 5 years (Table 4) It seems permissible to assume that moderate or massive degrees of elastosis occur in slowly progressing tumours Only a few sections from each tumour were examined, however, and the degree of elastosis may have been underestimated in some cases

Relatively few patients, together constituting about 15 per cent of the total series, could be assigned to prognostically distinct groups according to microscopic classification Pure colloid carcinomas were excluded from the material Papillary or cribriform appearances in a ductal carcinoma implied a relatively good prognosis (Table 7) as observed also by HAAGENSEN (1971) The small group of comedo carcinoma was found to have a poorer prognosis than other types (Table 7) HULTBORN & TÖRNBERG (1960) reported similar findings In the present material carcinomas were classified as comedo type when the microscopic appearance was that of solid, intraductal growth with central necrosis, irrespective of the relative amounts of the intraductal and the invasive parts This may explain some of the discrepancy between the present findings and those reported by McDIVITT et coll (1968) They found a higher survival rate in comedo carcinoma in a series consisting of predominantly intraductal carcinoma In medullary carcinoma with lymphoid infiltration the survival rates in the present material were not different from those of other tumour types (Table 7) Like McDIVITT et coll it was found that after 5 years [illegible]

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SUMMARY

The simultaneous prognostic influence of multiple clinical and microscopic features of mammary carcinoma was analysed in 581 women with radical mastectomy The most important of these features were connected with the extent of the disease in the axillary lymph nodes In substantial groups of patients however a favourable outcome could be predicted from microscopic features of the primary tumour viz. tubule formation mitotic frequency and elastosis

ZUSAMMENFASSUNG

Die simultane prognostische Einwirkung von mehreren klinischen Merkmalen und dem mikroskopischen Aussehen des Mammakarzinoms wurde bei 581 Frauen nach radikaler Mastektomie untersucht Die wichtigsten dieser Parameter waren zur Ausbreitung der Krankheit in den axillären Lymphknoten verbunden In bedeutenden Gruppen von Patienten konnte jedoch eine gunstige Prognose nach dem mikroskopischen Aussehen des Primärtumors wie Tubulusformation Mitosenfrequenz und Elastosis vorausgesagt werden

RESUME

Sur 581 femmes traitees par mastectomie radicale les auteurs ont étudié l influence pronostique simultanee de nombreux caracteres cliniques et microscopiques du cancer du sein. Les plus importants de ces caracteres eta ent en rapport avec l extension de la maladie dans les ganglions lymphatiques axillaires Cependant dans des groupes importants de malades on peut prevoir un pronost c favorable a partir des caracteres microscopiques de la tumeur primitive en particulier la formation de tubules la frequence des mitoses et l elastose

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increasing lymphoid infiltration It has been shown that breast tumours of high grade malignancy are more likely than less malignant tumours to be infiltrated by lymphoid cells (SCHIODT 1966, CHAMPION et coll 1972, FISHER et coll 1975) On the other hand, some tumours with extensive lymphoid infiltration do better than might be expected (McDIVITT et coll 1968)

The clinical variables explained little of the variance of survival (Table 6) However, since the selection of the patients for radical surgery was based mainly on the clinical findings, some of the explanatory values of these predictors had already been exploited

The available predictors at the time of radical mastectomy accounted for little of the variance in survival of the patients who were alive after 5 years Most of the intergroup differences in ten-year rates arose from differences which were already established at 5 years

The explanatory values of the AID analyses were fairly low (Table 6) From the clinical standpoint, however, the possibility of detecting groups of cases in which the outcome may be predicted with a high level of reliability is more important In contrast to other techniques for multivariate analysis, such as multiple regression, AID analysis leads to a number of subgroups which often are more homogeneous than the original sample with respect to the dependent variable But since each partitioning represents only one of all the possible splits, the largest possible subgroup with a high or a low value for the dependent variable may remain undetected The analyses disclosed a number of subgroups with a favourable outcome (Table 5, Figs 2 to 5) The 124 patients with highly or moderately regular tubule formation had 95 per cent five-year and 86 per cent ten-year survival (Table 5, Fig 3) Of these patients, none with moderate or massive elastosis in the tumour died of the malignancy during the first 5 years after radical mastectomy (Fig 2) In cases with poor tubule formation or non-tubular type of carcinoma and few mitoses the ten-year survival rate was 93 per cent (Fig 4) In a group of 89 patients who had had symptoms or signs for more than 3 months, whose tumours did not exceed 2 cm and who had at most one macrometastasis, 95 per cent were still alive after 10 years (Fig 5)

On the other hand, no substantial group with decidedly bad prognosis was revealed The poorest results were found in 38 patients with 2 or more involved axillary nodes, and massive perinodal growth and whose primary tumours measured more than 2 cm or were multiple Their ten-year survival rate was 13 per cent Of 150 patients with two or more involved axillary nodes and tumours with no or poor tubule formation, 34 per cent were alive after 10 years (Fig 5)

The possibility of identifying prognostically distinct groups without the information provided by microscopy of axillary lymph nodes is especially relevant when less radical surgical procedures, such as simple mastectomy or excision of tumour, are contemplated The present analysis has demonstrated that the clinical predictors and the microscopic features of the primary tumour provide a poor basis for recognizing groups with bad prognosis but permit prediction of a favourable outcome for substantial groups of patients

FROM THE DIVISION OF RADIATION ONCOLOGY, UNIVERSITY OF VIRGINIA MEDICAL CENTER, CHARLOTTESVILLE VA 22901, U S A

RESULTS OF IRRADIATION OF TUMORS IN THE REGION OF THE PINEAL BODY

N J SMITH, A M EL-MAHDI and W. C CONSTABLE

Tumors in the region of the pineal body are rare, occurring as 0 5 to 1 0 per cent of all intracranial tumors (ZULCH 1965) Young males are most often affected (DAYAN et coll 1966, NISHIYAMA et coll 1966, RUSSELL & RUBINSTEIN 1971) A presumptive diagnosis is usually made on clinical and neuroradiologic findings Although treatment has varied from center to center, radiation therapy has usually been an integral part of the planned management However, there have been a few long term survivors following only a shunting procedure (TORKILDSEN 1948)

Early reports of surgical excision were disappointing DANDY (1936) reported seven consecutive deaths among 10 patients where radical extirpation was attempted Subsequently, HORRAX (1950), RAND & LEMMEN (1953) and RINGERTZ et coll (1954) each reported high operative mortality in their series Due to an unfavorable experience with radical surgery, DAVIDOFF (1967), POPPEN & MARINO (1968) and RAND

a significant number of long term survivors with radiation therapy as the primary treatment modality Although there are a few recent reports showing that radical excision of pineal tumors may be accomplished with reasonable safety (STERN

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Submitted for publication 23 April 1975

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Table

Frequency of presenting signs and symptoms

	Per cent
1) Symptoms secondary to increased intracranial pressure	85
2) Spasticity	35
3) Ataxia	30
4) Parinaud's syndrome	25
5) Nystagmus (cerebellar type)	25
6) Syncope	20
7) Vertigo	20
8) Cranial nerve palsy (other than C.N. VI or VII)	20
9) Intention tremor	15
10) Scotoma	10
11) Tinnitus	10
12) Other	10

et coll. 1971 and SUZUKI & IWABUCHI 1965), the value of radiation therapy continues to be emphasized.

The effectiveness of irradiation in relieving symptoms and increasing survival at this center is now reported.

Material and Methods

Records of all patients with tumors in or about the third ventricle, sella, midbrain, and brainstem from the period 1950 through 1969 were reviewed. Among these patients, 20 previously untreated patients (15 males ranging in age from 2 months to 65 years, and 5 females from 22 to 58 years) had tumors in the region of the pineal body. The most common presenting symptom was that associated with increased intracranial pressure. The frequency of presenting signs and symptoms is given in the Table. The duration of symptoms ranged from 2 weeks to 3 years with 76 per cent of patients presenting within 6 months of the onset of symptoms.

Diagnosis was presumed on the basis of encephalography in one patient and on pneumoventriculography in the remaining patients. In addition, 5 patients had surgical exploration of the cerebellum and brain stem, although in no case was an attempt made to excise or biopsy the tumor. Radiologically, however, all patients had filling defects in the midline of the posterior part of the third ventricle consistent with pinealoma.

Throughout this review period, the treatment policy was decompression and ventricular shunting if necessary, followed by radiation therapy in all patients whose general condition allowed it. Of the 20 patients, 2 patients did not require a shunting

procedure Among the 20 patients reviewed, 14 were accepted and received a planned course of radiation therapy These 14 patients are thus available for analysis

All patients were prescribed to receive a tumor dose of 4 000 rad or higher Initially, 200 kV radiation with multiple portals was used, and later ^{60}Co teletherapy with parallel opposed or three fields Irradiation was administered with an average tumor dose of 200 rad per treatment 5 times per week, and all fields were treated daily Field size was usually 25 cm² to 50 cm², although an occasional patient with an advanced tumor was treated with portals up to 100 cm² No prophylactic irradiation to the entire cerebro-spinal axis was given Retreatment was attempted in 5 patients Doses were then reduced to 1 000 to 2 000 rad

Results

Among the 14 patients treated, signs and symptoms attributable to increased intracranial pressure such as diplopia, blurred vision and headache were relieved by a shunting procedure alone Eleven patients (79 %) had significant improvement from the course of irradiation, as determined by relief of other neurologic signs and symptoms and by survival Signs attributable to brain stem involvement were relieved in 7 of 8 patients Cerebellar signs improved in one of 3 patients In no case was Parinaud's syndrome relieved

Six patients died or were lost to follow up within 3 years Eight patients survived more than 3 years with minimal residual neurologic deficit One of these patients developed a spinal metastasis 3½ years after treatment The remaining 7 patients (50 %) survived 5 years or more

Visual abnormality and brain stem involvement occurred with approximate equal frequency among survivors as in the entire group However, only one patient of 8 presenting with cerebellar signs in the entire group is among the long term survivors This patient improved following radiation therapy and remained stable for 11 years with mild ataxia She died without clinical evidence of recurrence though no autopsy was obtained Hypothalamic involvement was present in one patient initially who later was in such poor condition as not to complete treatment, and occurred in a second patient as a terminal event

Two patients developed metastases One had seeding within the third ventricle on presentation and is presently alive at 5 years with no evidence of disease The other developed a local recurrence and spinal metastasis 3½ years after treatment, dying shortly thereafter

In the 5 patients where retreatment was attempted it was successful in one and palliative in two

Discussion

Malignant tumors in the midline and posterior part of the third ventricle may be distinguished by neuroradiologic methods and include tumors of the pineal body,

Table

Frequency of presenting signs and symtoms

	Per cent
1) Symptoms secondary to increased intracranial pressure	85
2) Spasticity	35
3) Ataxia	30
4) Parinaud s syndrome	25
5) Nystagmus (cerebellar type)	25
6) Syncope	20
7) Vertigo	20
8) Cranial nerve palsy (other than C N VI or VII)	20
9) Intention tremor	15
10) Scotoma	10
11) Tinnitus	10
12) Other	10

et coll 1971 and SUZUKI & IWABUCHI 1965), the value of radiation therapy continues to be emphasized.

The effectiveness of irradiation in relieving symptoms and increasing survival at this center is now reported

Material and Methods

Records of all patients with tumors in or about the third ventricle, sella, midbrain, and brainstem from the period 1950 through 1969 were reviewed Among these patients, 20 previously untreated patients (15 males ranging in age from 2 months to 65 years, and 5 females from 22 to 58 years) had tumors in the region of the pineal body The most common presenting symptom was that associated with increased intracranial pressure The frequency of presenting signs and symptoms is given in the Table The duration of symptoms ranged from 2 weeks to 3 years with 76 per cent of patients presenting within 6 months of the onset of symptoms

Diagnosis was presumed on the basis of encephalography in one patient and on pneumoventriculography in the remaining patients In addition 5 patients had surgical exploration of the cerebellum and brain stem, although in no case was an attempt made to excise or biopsy the tumor Radiologically, however, all patients had filling defects in the midline of the posterior part of the third ventricle consistent with pinealoma

Throughout this review period, the treatment policy was decompression and ventricular shunting if necessary, followed by radiation therapy in all patients whose general condition allowed it Of the 20 patients, 2 patients did not require a shunting

no sex or age predominance (RUSSELL & RUBINSTEIN) and may contribute to the broad age distribution in this as well as other series. Teratomas may be typical and include all three germ layers or atypical closely resembling seminoma or dysgerminoma. The atypical group comprises the majority of tumors in this region (ALBRECHTSEN et coll 1972, FRIEDMAN 1947 and RUSSELL & RUBINSTEIN) is predominantly found in males and has a peak incidence in the second decade of life. Its microscopic similarity to radiation sensitive tumors of the testicle and ovary may account for successful treatment with radiation (NISHIYAMA et coll 1966). Due to the variety of possible histologic types it appears that a dose around 5 000 rad using conventional fractionation is optional for treatment (EL MAHDI et coll. 1972). The incidence of spinal metastases seems sufficiently low to justify treating with small fields sparing as much normal tissue as possible (MAIER & DEJONG 1967).

SUMMARY

The clinical findings and results of radiation treatment in 14 patients with tumors in the region of the pineal body are presented. The neurologic signs and symptoms improved significantly in 11 patients (79 per cent). The survival rate for five years or more was 50 per cent. Radiation therapy as the primary method of treatment is discussed.

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oder länger betrug 50%. Die Strahlentherapie als primäre Behandlungsmethode wird diskutiert.

RESUME

Les auteurs présentent les tableaux cliniques et les résultats du traitement par les radiations chez 14 malades atteints de tumeur de la région pinéale. Les signes neurologiques et les signes fonctionnels ont été améliorés de façon importante chez 11 malades (79%). Le taux de survie à 5 ans ou plus a été de 50%. Les auteurs étudient le traitement par les radiations comme méthode de traitement primaire.

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colliculate plate, and aqueduct (GREITZ 1972) Differentiation among these sites is difficult, and was not attempted in this series However, benign tumors (colloid cysts) are reliably excluded by proper neuroradiologic assessment (CUMMINGS et coll 1966), and many series presume the diagnosis of pineal tumors short of surgical *exploration of the third ventricle*

The histories of 20 previously untreated patients fitting this criteria and presenting from 1950 to 1969 have been reviewed Six were in such poor general condition that a course of irradiation was not possible The remaining 14 patients completed a course of radiation therapy Fifty per cent of these have survived 5 years or more

A review of the literature shows that the *surgical mortality may be high and that* most survivors have received radiation therapy following radical extirpation Decompression, when necessary, followed by radiation therapy has produced equal or improved survival without the morbidity or mortality of extirpation

An analysis of the frequency of presenting signs and symptoms was made to *predict* prognosis, and to evaluate the response to radiation therapy Visual disturbance is a frequent initial presenting symptom Classically, there is a paresis of upward gaze (Parinaud's syndrome) Insofar as paresis of upward gaze is secondary to a destructive *process in the midbrain tegmentum (BALTHASAR 1968), it might not be expected to* be relieved by treatment and was not relieved in any of the patients demonstrating it in this series Other visual disturbances such as diplopia and blurred vision are not uncommon and were mainly improved by decompression Evidence of brain stem involvement including cranial nerve paresis and spastic hemiparesis were frequent presenting findings and were improved in most cases with treatment The presence of visual disturbance or brain stem involvement was not unfavorable prognostic findings in this series They occurred with equal frequency among survivors as in the entire group

Eight patients in the entire group presented with evidence of cerebellar dysfunction (ataxia or intention tremor) Only 3 of them were able to undergo a course of irradiation and one survived Although the numbers are small, this suggests that cerebellar signs or symptoms unfavorably affect prognosis, possibly due to greater tumor size

Disorders of hypothalamic and neurohypophyseal function may also be initial findings, and were found in one patient in this series (diabetes insipidus) who died before treatment A second patient developed diabetes insipidus terminally No prognostic *interpretation can be made, although most other reported* cases continue to require exogenous hormonal replacement following irradiation (PUSCHETT & GOLDBERG 1968)

Failure to achieve a satisfactory response to radiation therapy *in some of these* patients may [illegible] due to the variety of histologic types in this region RUSSELL & RUBINSTEIN (197[illegible] divide tumors of the posterior part of the third ventricle into four categories (1) pinealoma, (2) teratoma, (3) glioma and (4) cysts True pinealomas (pineocytoma and pineoblastoma) of pineal parenchymal origin account for only 20 per cent of all tumors of the pineal body (MCGOVERN 1949) They are stated to have

FROM RADIUMHEMMET, KAROLINSKA SJUKHUSET, AND THE DEPARTMENT OF TUMOR BIOLOGY, KAROLINSKA INSTITUTET, S-104 01 STOCKHOLM, SWEDEN

IN VIVO AND IN VITRO SELECTION OF MITOGEN RESPONSIVE LYMPHOCYTES IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

H Blomgren, M Jondal and B Johansson

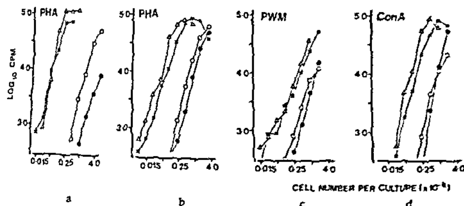
The immunologic reactivity of peripheral lymphocytes, from patients with various types of malignancies as reflected by their proliferative response to polyclonal [illegible]

[illegible] (Whittaker et coll 1970, Blomgren et coll 1974 b), bowel (Watkins 1973), brain (Brooks et coll 1972), lung (*Hann & Takita 1972*, Ducos et coll 1970) and Hodgkin's disease (Cohnen et coll 1973, Trubowitz et coll 1966) The reason for the low responsiveness of their lymphocytes is unknown

Peripheral lymphoid cells of patients with chronic lymphocytic leukemia (CLL) usually have an extremely poor mitogen response, on a cell-for-cell basis in vitro (Quaglino & Cowling 1964, *Trubowitz et coll*, Thomson et coll 1966, Havemann & Rubin 1968, Catovsky et coll 1972, König et coll 1972) These patients frequently have highly increased numbers of lymphoid cells in the blood, mostly bearing immunoglobulins of the same class on the outer membrane (Johansson & Klein 1970, Klein et coll 1970, Eskeland et coll 1971) This indicates that they have a monoclonal tumor origin

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centration of 1.0 × 10⁶ cells/ml. After 24 h the cultures were centrifuged and the supernatants stored at −20 C before use.

Mitogen responses of lymphocytes were measured in vitro using culture conditions described previously (BLOMGREN et coll. 1974 b). In short, various numbers of lymphocytes were cultured in glass tubes containing 1.0 ml of MEM with penicillin, streptomycin and 10% of HS. In those tests where the mitogen reactivity of separated and non-separated populations of cells from CLL were compared 0.5 ml of 'conditioned media' and 0.5 ml of fresh MEM containing penicillin, streptomycin and HS were used. Half of the cultures received a stimulant and the others served as controls. After four days of incubation at 37°C in a humidified 5% CO_2-air atmosphere each culture received 0.4 μCi of ^{14}C-thymidine. Twenty-four h later the cultures were terminated and the activity of acid precipitable material determined by means of a liquid scintillation counter (Packard).

The incorporated activity was expressed as counts per minute (cpm). Isotope incorporations obtained in control cultures without mitogen were subtracted from the values obtained in corresponding cultures exposed to mitogens. Mean values from duplicate cultures were calculated on a geometric basis and expressed as $\log_{10}$ cpm.

Because of the extensive variability of the mitogen responses of human lymphocytes, from time to time the lymphocytes of a healthy control were always tested in parallel with patient cells. A patient tested on several occasions had the same control subject throughout the observation period. The lymphoid cells of patients and controls were incubated at several different concentrations with and without mitogen. Cells from CLL patients were cultured at two-fold dilutions of 8.0 × 10⁶ cells/ml to 1.2 × 10⁵ and cells from the controls and a patient with lymphoma were cultured at cell con-

In the present investigation is tested whether highly mitogen responsive lymphocytes can be separated from the blood of patients with CLL by a buoyant density centrifugation technique and whether such cells are enriched after splenic irradiation or chemotherapy

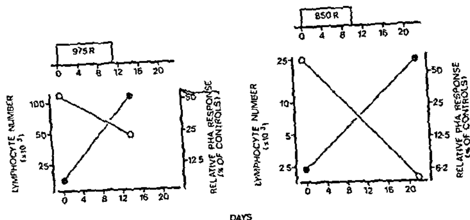
Material and Methods

Eight patients with CLL or malignant lymphoma were examined No patient had received any specific therapy at the time of the first test of their peripheral lymphocytes Healthy members of the laboratory staff, 25 to 30 years old, served as donors of control lymphocytes

Lymphoid cells from venous blood, drawn in heparinized syringes, were separated by centrifugation on a Ficoll-Isopaque gradient as described previously (JONDAL et coll 1972) The cells were washed twice by centrifugation in Eagle's Minimal Essential Medium (MEM) These cell suspensions will hereafter be designed non-purified In some experiments T-lymphocytes were separated from the non-purified suspensions by the method of JONDAL (1974 a) In short, 0 4 g of carbonyl iron powder was added to 5×10^{8}–10^{9} lymphoid cells suspended in 10 ml of MEM The suspensions were gently shaken every 5 min during incubation at 37° for 45 min They were then cleared of iron particles and iron-containing cells with a powerful magnet The resulting cell suspensions were incubated with sheep erythrocytes (SRBC) During this step SRBC will non-specifically adhere to T-cells present in the cell preparations (JONDAL et coll) These were then suspended in fetal calf serum, previously heated at 80° for 30 min, and centrifugated on a Ficoll-Isopaque gradient The T-cell-SRBC complexes sediment due to their increased density, whereas other nucleated cells remain at the fluid interphase These two cell populations were collected and contaminating SRBC lysed with ammonium chloride The cells which sediment will hereafter be termed T-cells and the cells at the fluid interphase non-T-cells Cells numbers and viability was determined in a Burker chamber after trypan blue staining

The lymphoid cells were stimulated with the following phytomitogens (a) Phytohaemagglutinin (PHA, Bacto Phytohaemagglutinin M, Difco Lab , Detroit, Mich) The contents of a vial containing PHA was dissolved in 5 ml of MEM This solution will be referred to as 100 % PHA, (b) Concanavalin A (ConA, Sigma Chemical Co , St Louis, Mo) was dissolved in MEM, (c) Poke weed mitogen (PWM, Grand Island Biological Co , NY) The contents of a vial containing PWM was dissolved in 5 ml of MEM This solution will be referred to as 100 % Lymphocytes were stimulated with these agents at the following final concentrations 3 % of PHA, 0 22 % of PWM and 28 μg of ConA per ml

Conditioned media were produced by incubating non purified lymphocyte preparations from healthy donors in MEM containing 100 units of penicillin, 150 μg of streptomycin per ml and 10 % of human serum (HS) The HS was previously decomplemented by heating at 56°C for 30 min The cells were cultured at a con-



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cells per μl blood O—O, PHA reactivity of the cells ●—●

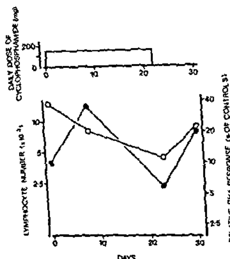


Fig 3 Effect of cyclophosphamide treatment of a patient with CLL on the number of lymphoid cells in peripheral blood and their relative response to PHA The period of chemotheraphy is indicated in the figure Number of lymphoid cells O—O, PHA reactivity of the cells ●—●

for case 1 The total skin dose of 850 R was fractionated over 10 days, giving 250 rad at a depth of 10 cm The lymphoid counts were reduced to approximately 1 800 (*Fig 2, right diagram*) and the relative mitogen reactivity of the cells increased ten fold

Patients receiving chemotherapy

Case 3 An 85-year-old man with CLL Peripheral lymphoid cell counts moderately elevated The patient was *treated with 150 mg* of cyclophosphamide (Sendoxan, Pharmacia, Uppsala, Sweden) administered orally for 22 days This therapy resulted *in a decreased*

centration of 1 0 × 10⁶ to 7 0 × 10³ per ml The isotope incorporations were plotted on semilogarithmic scales This yielded roughly linear increases of thymidine uptakes within certain dose ranges of cells (Fig 1) The horisontal distance between the dose response lines obtained from lymphocytes from the control and the patient was measured to calculate the difference in relative mitogen responsiveness of the two cell populations Since the slopes of the lines differed in some tests, the difference at those points of the curves corresponding to an isotope incorporation of 4 00 $\log_{10}$ units, was always calculated Mitogen responsiveness of the patient's lymphocytes were related to that of the control's and expressed as per cent

Results

Enrichment of mitogen responsive cells from the blood of CLL The mitogen responses of peripheral lymphoid cells from three CLL patients and a control appear in Fig 1 The response of unseparated CLL cells was lower, on a cell-for-cell basis, than that of the control lymphocytes in all four tests However, separated T-lymphocytes from the CLL populations exhibited almost the same responses to all three mitogens as the control lymphocytes On the contrary, non-T-lymphocytes obtained at the fluid interface of the buoyant density gradient were less mitogen reactive than the original unseparated CLL preparation

Relative mitogen responses of peripheral lymphocytes before and after therapy The results described strongly indicate that there is a subpopulation of normally mitogen responsive T-lymphocytes in the blood of CLL Furthermore, the data support the view that CLL lymphocytes are non-responsive to phytomitogens It was of interest to know whether treatment of patients with CLL, aiming at reducing the tumor cell population, results in an enrichment of non-neoplastic, mitogen responsive lymphocytes

Thus, 4 patients with CLL and one with a malignant lymphoma were examined for in vitro lymphocyte response to PHA

Patients receiving splenic irradiation

Case 1 A 56 year-old man with a newly diagnosed CLL with more than 100 000 lymphoid cells per μl of blood The patient received conventional external roentgen irradiation over the spleen, which was enlarged The irradiated skin field measured 15 cm × 14 cm, and a total exposure dose of 975 R was delivered over 11 days (196 kV, 20 mA, FSD 70 cm, added filter 0 4 mm Sn 0 25 mm Cu and 1 0 mm Al) This gives a tissue dose of approximately 400 rad at 10 cm depth which was estimated to be the mid-point of the spleen The number of lymphoid cells decreased from 120 000 to 50 000 (Fig 2, left diagram) and the relative PHA response of the cells increased by a factor of 6

Case 2 A 58-year old man with a newly diagnosed CLL with 35 000 lymphoid cells per μl of blood The patient received conventional roentgen irradiation over the enlarged spleen The field measured 19 cm × 12 cm, and the radiation parameters were the same as

pared to lymphoid cells from healthy donors, and the other is that there exist normally responsive lymphocytes in CLL which are mixed with a large pool of cells which are non responsive to phytomitogen lectins Since the majority of the peripheral lymphoid cells of CLL patients have surface associated Ig, which is a characteristic for B lymphocytes, it is likely that the second alternative is correct It has namely been observed that B cells from normal subjects exhibit poor proliferative response to phytomitogens, whereas T-cells respond strongly (PHILLIPS & ROITT 1973, 1974, GREAVES et coll 1974) For a review of T- and B lymphocytes is referred to ROITT et coll (1969)

In the present investigation T-lymphocytes were separated from the peripheral blood of CLL patients Enrichment of these cells was achieved by a buoyant density centrifugation after rosetting the cells with SRBC in vitro The cell suspensions were always cleared from macrophages, monocytes and other phagocytic cells before differential centrifugation of the cell suspensions Since the mitogen response of human lymphocytes is strongly enhanced in the presence of soluble factors released by such cells (GERY et coll 1972, OPPENHEIM et coll 1968), the cell preparations were cultured in a medium, conditioned by peripheral lymphocytes, containing both monocytes and macrophages Such conditioned media markedly enhance the mitogen response of lymphocyte preparations cleared from monocytes—macrophages but not unpurified cell suspensions (BLOMGREN et coll 1974 a) Under these culture conditions the relative responses of enriched T-lymphocytes in CLL to PHA, PWM and ConA were approximately the same as the response of lymphocytes from normal healthy subjects It may be argued that the responses of the lymphocytes from the controls were falsely low because they did not constitute separated T-cells However, separated T cells from normal subjects are only marginally increased compared to unseparated cell populations (JONDAL 1974 b) Moreover, the donors of control lymphocytes were younger than the CLL patients The frequency of PHA-responsive T cells has been found to decrease with increasing age of the cell donors with the exception of lymphocytes from newborn individuals (SMITH et coll 1974) The findings that the cells harvested at the fluid interphase after density centrifugation, mainly non T-lymphocytes, exhibited a lower mitogen response than unfractionated cells from CLL, supports the concept that the lymphoid cells of such patients consist of one large mitogen unresponsive and a small strongly mitogen responsive population of cells This conclusion is in agreement with the results of other investigations demonstrating that cells with increased mitogen reactivity can be separated from the blood of CLL by differential centrifugation (SCHWEITZER et coll 1973, WYBRAN et coll 1973) or by removal of Ig bearing cells by passage through column beads coated with human Ig and rabbit anti human Ig serum (BLOMGREN et coll 1974 a)

Treatment of CLL patients aims at reducing the number of neoplastic lymphoid cells This treatment should thus theoretically result in an increased frequency of normal, non neoplastic lymphocytes ZUCKER & CASSEN (1974) have observed that cyclophosphamide treatment of CLL patients results in an almost selective reduction

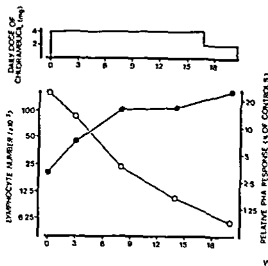


Fig 4

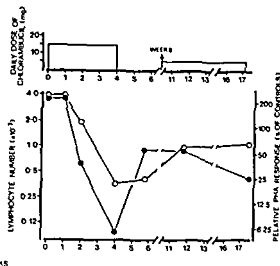


Fig 5

presented in Fig 3

number of lymphoid cells in the blood (Fig 3) During the early stage of the treatment the relative PHA activity of the cells increased However, continued therapy decreased the responsiveness of the cells below the initial value This impaired response was only transient as the reactivity increased after termination of treatment

Case 4 A 70-year-old woman with CLL Peripheral lymphoid cell counts highly increased The patient was treated with chlorambucil (Leukeran, Burroughs Wellcome & Co , London, England) administered orally at daily doses of 4 or 2 mg The number of lymphoid cells in the blood decreased during the entire observation period (Fig 4) The relative mitogen response of the cells increased during this period, but not to the same extent as would be expected if there was a selective reduction of leukemic cells

Case 5 A 61-year-old woman with a desiminated malignant lymphoma without evidence of neoplastic cells in peripheral blood The patient was treated with chlorambucil orally at daily doses of 15 or 5 mg

This patient was tested to examine the effect of chlorambucil treatment on the mitogen reactivity of normal, non malignant lymphoid cells in peripheral blood The lymphocyte counts were sharply decreased during the first 4 weeks when the patient obtained 15 mg daily of this drug (Fig 5) During this period there was also a sharp decrease of the relative PHA reactivity of the cells Mitogen responsiveness was increased shortly after termination of the treatment in spite of the fact that the lymphocyte number remained approximately on the same level The second treatment with the same drug, but in a smaller dose, caused a slight decrease of PHA reactivity but not the cell number

Discussion

There are two different explanations of the low mitogen responsiveness of CLL lymphoid cells in vitro One is that the mitogen reactivity per cell is decreased com-

RÉSUMÉ

Les auteurs ont constaté que la reponse mitogénique in vitro des cellules lymphoïdes sanguines de malades atteints de leucemie lymphocytaire chronique est moins intense que celle de lymphocytes de sujets sains Cependant une technique de centrifugation à densité legere a permis d'isoler dans le sang de ces malades des cellules à réponse mitogenique elevee, la chimiothérapie ou l irradiation splenique de ces malades augmente le nombre de ces cellules reagissant fortement

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of small lymphocytes with a high density, whereas prednisolone acted nonselectively on the cells They presented evidence indicating that these small lymphoid cells are leukemic In the present investigation it was observed that chemotherapy of a CLL patient with cyclophosphamide or chlorambucil resulted in an increased relative PHA response of the peripheral lymphocytes This strongly indicates that these agents destroy leukemic cells to a higher extent than normal lymphocytes However, the effect is not completely selective, since the PHA reactivity was found to be decreased after prolonged treatment of a CLL patient with comparatively low initial lymphocyte numbers Similarly, it was observed that chlorambucil treatment of a patient with malignant lymphoma, without evidence of neoplastic cells in the blood, resulted in a decreased number of lymphoid cells with a concomitant reduction of PHA reactivity This low responsiveness, induced by chemotherapy, was of short duration and reactivity reappeared soon after termination of therapy The results also revealed that splenic irradiation of CLL patients almost selectively reduces the pool of malignant cells from the blood, leaving the normal lymphocytes relatively untouched

In conclusion, this investigation has demonstrated that there exists a population of highly mitogen responsive lymphocytes in the blood of untreated CLL The frequency of such cells may increase in the blood after treatment of the patient with chemotherapy or irradiation

Acknowledgements

The authors wish to thank Miss Harriet Blomquist and Miss Marja Rikkinen for their excellent technical assistance This work was supported by grants from the Cancer Society in Stockholm and from the Swedish Cancer Society

SUMMARY

The in vitro mitogen response of blood lymphoid cells from patients with chronic lympho cytic leukemia was observed to be low compared to lymphocytes from healthy subjects However, highly responsive cells could be separated from the blood of such patients by a buoyant density centrifugation technique and such reactive cells were found to be enriched by treating the patients with chemotherapy or splenic irradiation

ZUSAMMENFASSUNG

Die in vitro mitogene Reaktivitat von Blut lymphoiden Zellen von Patienten mit chro nischer lymphatischer Leukamie erwies sich im Vergleich zu Lymphozyten von normalen Personen als niedrig Es konnten jedoch hoch reaktive Zellen vom Blut derartiger Patienten durch eine spezielle Zentrifugierungstechnik gewonnen werden und derartige reaktive Zellen wurden bei Behandlung von Patienten mit Chemotherapie oder Milz Bestrahlung angereichert

RÉSUME

Les auteurs ont constate que la reponse mitogénique in vitro des cellules lymphoides sanguines de malades atteints de leucémie lymphocytaire chronique est moins intense que celle de lymphocytes de sujets sains Cependant une technique de centrifugation a densité legere a permis d isoler dans le sang de ces malades des cellules à réponse mitogenique élevée la chimiotherapie ou l irradiation splenique de ces malades augmente le nombre de ces cellules réagissant fortement

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DNA-SYNTHESIS OF LYMPHOCYTES IN HYPERTHYROID AND EUTHYROID SUBJECTS

Effect of ^{131}I therapy on hyperthyroidism

G LUNDELL J WASSERMAN, NINA EINHORN and P O GRANBERG

Treatment of hyperthyroidism with radioiodine is followed by an increase in circulating cytoplasmic thyroid antibodies (BUCHANAN et coll 1962, O GORMAN et coll 1964 IRVINE 1964 EINHORN et coll 1965, 1966, JONSSON et coll 1968) Moreover, patients who develop hypothyroidism after such treatment have a significantly higher frequency of positive serologic reactions (EINHORN et coll 1965, LUNDELL & JONSSON 1973) These findings motivated an investigation of possible changes in cellular immunity The spontaneous DNA synthesis of lymphocytes was evaluated by measurements of the incorporation of isotope labelled thymidine in vitro before and after ^{131}I therapy This synthesis was considered to reflect at least to a certain extent the proliferative potential of the cells In addition, the response of lymphocytes in the presence of thyroglobulin in vitro was examined

It has been stated previously (EINHORN et coll 1971) that ^{131}I treatment for hyperthyroidism is followed by an increase in lymphocyte reactivity to thyroglobulin In the present report this statement is re evaluated and the implications arising from the data presented are discussed

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Table 1

Incorporation of ^{14}C thymidine by lymphoid cells in vitro before and after ^{131}I therapy for hyperthyroidism The mean value for all 42 patients before therapy was 2405 ± 440 cpm

Interval after ^{131}I therapy	No of pat	No of tests	Change in thymidine incorporation after therapy No of cases		Mean of individual differences in thymidine incorporation cpm		Significance of the difference, p
			Increase	Decrease	Mean	SE	
6 weeks 3 months	30	32	9	21	−1 265	619	<0 05
4–6 months	31	34	12	19	−1 245	617	NS
7 12 months	35	47	14	21	−1 247	469	<0 05
13–18 months	33	35	13	20	−1 126	419	<0 05
19 24 months	31	34	11	20	− 623	500	NS
≥25 months	22	22	4	18	−1 305	504	<0 05

Table 2

Incorporation of ^{14}C thymidine by lymphoid cells in vitro before and after ^{131}I therapy for hyperthyroidism The mean value for all 9 patients before therapy was 4 981 ± 1 335 cpm

Interval after ^{131}I therapy	No of pat	No of tests	Change in thymidine incorporation after therapy No of cases		Mean of individual differences in thymidine incorporation cpm		Significance of the difference p
			Increase	Decrease	Mean	SE	
6 weeks-3 months	6	8	1	5	2 153	2 412	NS
4–6 months	6	7	0	6	3 692	1 876	NS
7 12 months	6	9	0	6	4 056	1 444	<0 05
13 18 months	4	4	0	4	5 118	844	<0 01

positive Rh negative donors One or two million cells, as indicated in the text, were pipetted into conical tissue-culture tubes The total volume of the incubation m[illegible] was 1 ml Th[illegible] flow of a [illegible] (specific a[illegible] [illegible] Radiochemical Centre, Amersham, England) was added to all tubes Twenty four hours later the cultures were completed by centrifugation in the cold and the addition of trichloracetic acid The amount of incorporated isotope was determined by a Packard scintillation counter Duplicate cultures were performed and mean ^{14}C thymidine incorporation expressed as counts per minute (cpm) and the SE were calculated Moreover, mean values of individual differences between cpm obtained before and at different time intervals after therapy were calculated in all patient groups

Material

The material consisted of three groups of patients and one group of controls

Group A 42 hyperthyroid patients, 36 females and 6 males, aged 29 to 78 years (mean 57 years), treated with ^{131}I during the period 1969 to 1970 Nineteen had diffuse and 23 nodular goitres and all belonged to a material presented previously (EINHORN et coll 1971)

Group B 19 patients, all female, aged 22 to 63 years (mean 34 years), treated by surgery for hyperthyroidism during 1970 and 1971

Group C 18 patients, all female, aged 29 to 62 years (mean 45 years), with atoxic nodular goitre treated by surgery during 1970 and 1971

Group D (controls) 17 healthy volunteers receiving no treatment were examined by the same tests during the period of investigation There were 14 females and 3 males aged 24 to 49 years (mean 37 years)

The patients given ^{131}I therapy were treated according to the principles described by LARSSON (1955) and BELING & EINHORN (1961), the determination of thyroid function was made by the methods outlined by LUNDELL & JONSSON (1973) The patients were examined at intervals of 2 to 4 months during the first year and thereafter every year until the termination of this investigation, the minimum follow-up time being 3 years All patients treated for hyperthyroidism became euthyroid within this period

Patients belonging to group B were given antithyroid drugs and thyroxine preoperatively They were euthyroid at the time of surgery and at preoperative blood sampling *As a rule, bilateral subtotal thyroidectomy was performed in these patients* Postoperatively the patients with atoxic nodular goitre were given thyroxine routinely

Methods

Blood samples for the determination of DNA-synthesis in lymphoid cells were obtained at the clinical examinations before and after therapy

Venous blood for lymphocyte separation was defibrinated by gentle agitation in a beaker containing glass pearls Separation of the nucleated cells was performed by the method of COULSEN & CHALMERS (1964) The number of lymphoid cells was determined in a Burker chamber after crystal violet staining The cell suspensions used for the experiments regularly contained a minimum of 60 per cent lymphocytes

In 33 of the 42 patients in group A, 1×10^6 lymphoid cells were used at the beginning and since 1970 *2×10^6 cells In the remaining 9 patients 2×10^6 cells were used in all* tests In experiments with patients belonging to groups B and C, 2×10^6 cells were used Experiments with lymphocytes from individuals belonging to Group D were performed with 1×10^6 or 2×10^6 cells

The lymphoid cells were washed twice in Hank-Tris buffer and suspended in Eagle's medium supplemented with 10 per cent heat-inactivated serum from AB

Table 5

Healthy and euthyroid controls Incorporation of ^{14}C thymidine by lymphoid cells in vitro

Year of test	No of cells	Mean value cpm	SE	No of controls
1969/1970	1×10^6	1 000	189	12
1969/1970	2×10^6	1 813	396	12
1971	2×10^6	1 381	600	6

Table 6

Incorporation of ^{14}C thymidine by lymphoid cells in vitro in healthy controls and in patients before surgery or ^{131}I therapy 2×10^5 lymphoid cells

Group	Thyroid function at blood sampling	Planned treatment	No of subjects	Mean value cpm	SE	Significance of the difference to group A
A	Hyperthyroid	^{131}I	9	4 981	1 335	
B	Euthyroid	surgery	19	1 309	219	<0 001
C	Euthyroid	surgery	18	1 536	269	<0 01
D	Euthyroid	—	12	1 813	396	<0 05

within a specific time period In such cases the arithmetic mean of these tests was used in the statistical calculations

The statistical test used was the Student s t-test

Results

Spontaneous DNA-synthesis The mean value of the thymidine incorporation in lymphoid cells in group A decreased after therapy on all the occasions examined (Table 1) in comparison with the values of the same patient before therapy This was observed despite the fact that in 33 of the 42 patients 1×10^6 lymphoid cells were used before therapy and 2×10^6 cells after therapy The mean changes for the whole series were significant for the periods 6 weeks to 3 months ($p<0\ 05$), 7 to 12 months ($p<0\ 05$), 13 to 18 months ($p<0\ 05$) and more than 24 months after therapy ($p<0\ 05$) (Table 1) A significant decrease was also noted in the group of patients where 2×10^6 lymphoid cells were used throughout (Table 2)

In group B, no decrease was found in the DNA-synthesis as compared with the pre-treatment values (Table 3) These patients were, however, already euthyroid before surgery due to pre treatment with antithyroid drugs and thyroxine On the other hand, after surgery there was an increase in the DNA synthesis of lymphocytes at each time interval studied This increase, however, was not significant (Table 3) Similarly, after surgical treatment of atoxic nodular goitre, there was some increase

Table 3

Incorporation of ^{14}C thymidine by lymphoid cells in vitro before and after surgery for hyperthyroidism All 19 patients pretreated with antithyroid drugs and thyroxin and euthyroid upon examination before surgery At that time the mean value was 1 309 ± 219 cpm

Interval after surgery	No of pat	No of tests	Change in thymidine incorporation after surgery No of cases		Mean of individual differences in thymidine incorporation, cpm		Significance of the difference, p
			Increase	Decrease	Mean	SE	
6 weeks-3 months	12	12	6	6	1 151	757	NS
4–6 months	14	14	8	6	250	491	NS
7–12 months	15	24	10	5	1 027	523	NS
13–18 months	11	12	6	5	686	865	NS
19–24 months	3	3	1	2	428	1 154	NS

Table 4

Incorporation of ^{14}C thymidine by lymphoid cells in vitro before and after surgery for atoxic nodular goitre The mean value for all 18 patients before therapy was 1 536 ± 269 cpm

Interval after surgery	No of pat	No of tests	Change in thymidine incorporation after surgery No of cases		Mean of individual differences in thymidine incorporation, cpm		Significance of the difference, p
			Increase	Decrease	Mean	SE	
6 weeks–3 months	13	13	11	2	896	266	< 0 01
4–6 months	16	16	9	7	491	452	NS
7–12 months	14	22	10	4	959	463	NS
13–18 months	11	13	7	4	2 433	1 339	NS

Thyroglobulin was prepared from human thyroid tissue removed during surgery by the method of WEIBULL & LINDER (1960) Several batches, each from one single gland, were used Thyroglobulin as an antigen was added as 100 or 1 000 μg aliquots to each tube In the calculations, the value for 1 000 μg of thyroglobulin has been used throughout with the exception of those few cases in the series of 42 hyperthyroid patients where 100 μg was added The difference in stimulatory effect was small and in some cases higher with 100 μg than with 1 000 μg of thyroglobulin, which is consistent with the report of EINHORN et coll (1971) When calculating the stimulatory effect of thyroglobulin, the number of individual counts per minute for the spontaneous ^{14}C thymidine incorporation has been subtracted in order to estimate the effect of thyroglobulin on its own

In some patients the thymidine incorporation was determined more than once

Table 5

Healthy and euthyroid controls Incorporation of ¹⁴C thymidine by lymphoid cells in vitro

Year of test	No of cells	Mean value cpm	SE	No of controls
1969 1970	1×10^6	1 000	189	12
1969 1970	2×10^6	1 813	396	12
1971	2×10^6	1 381	600	6

Table 6

Incorporation of ¹⁴C thymidine by lymphoid cells in vitro in healthy controls and in patients before surgery or ¹³¹I therapy 2×10^6 lymphoid cells

Group	Thyroid function at blood sampling	Planned treatment	No of subjects	Mean value, cpm	SE	Significance of the difference to group A
A	Hyperthyroid	¹³¹I	9	4 991	1 335	
B	Euthyroid	surgery	19	1 309	219	$<0\ 001$
C	Euthyroid	surgery	18	1 536	269	$<0\ 01$
D	Euthyroid	—	12	1 813	396	$<0\ 05$

within a specific time period In such cases the arithmetic mean of these tests was used in the statistical calculations

The statistical test used was the Student's t test

Results

Spontaneous DNA-synthesis The mean value of the thymidine incorporation in lymphoid cells in group A decreased after therapy on all the occasions examined (Table 1) in comparison with the values of the same patient before therapy This was observed despite the fact that in 33 of the 42 patients 1×10^6 lymphoid cells were used before therapy and 2×10^6 cells after therapy The mean changes for the whole series were significant for the periods 6 weeks to 3 months ($p<0\ 05$), 7 to 12 months ($p<0\ 05$), 13 to 18 months ($p<0\ 05$) and more than 24 months after therapy ($p<0\ 05$) (Table 1) A significant decrease was also noted in the group of patients where 2×10^6 lymphoid cells were used throughout (Table 2)

In group B, no decrease was found in the DNA synthesis as compared with the pre treatment values (Table 3) These patients were, however, already euthyroid before surgery due to pre treatment with antithyroid drugs and thyroxine On the other hand, after surgery there was an increase in the DNA synthesis of lymphocytes at each time interval studied This increase, however, was not significant (Table 3) Similarly, after surgical treatment of atoxic nodular goitre, there was some increase

Table 7

Incorporation of ^{14}C thymidine by lymphoid cells in vitro in presence of thyroglobulin before and after ^{131}I therapy for hyperthyroidism The mean value for all 42 patients before therapy was 358±178 cpm, when the individual values obtained in the absence of thyroglobulin are subtracted

Interval after ^{131}I therapy	No of pat	No of tests	Change in thymidine incorporation after therapy No of cases		Mean of individual differences in thymidine incorporation cpm		Significance of the difference, p
			Increase	Decrease	Mean	SE	
6 weeks–3 months	20	21	13	7	33	222	NS
4–6 months	28	31	16	12	42	216	NS
7–12 months	35	46	20	15	118	228	NS
13–18 months	33	35	19	14	10	253	NS
19–24 months	31	34	17	14	− 1	174	NS
≥25 months	22	22	11	11	−109	286	NS

Table 8

Incorporation of ^{14}C thymidine of lymphoid cells in vitro in presence of thyroglobulin before and after surgery for hyperthyroidism All 19 patients pretreated with antithyroid drugs and thyroxine and euthyroid upon examination before surgery At that time the mean value was 257±99 cpm, when the individual values obtained in the absence of thyroglobulin are subtracted

Interval after surgery	No of pat	No of tests	Change in thymidine incorporation after surgery No of cases		Mean of individual differences in thymidine incorporation, cpm		Significance of the difference p
			Increase	Decrease	Mean	SE	
6 weeks–3 months	12	12	9	3	1 112	603	NS
4–6 months	14	14	10	4	434	251	NS
7–12 months	15	24	12	3	621	377	NS
13–18 months	11	12	6	5	111	261	NS

in the incorporation of thymidine in the lymphocytes, which was significant ($p<0\ 01$) during the period 6 weeks to 3 months after the operation (Table 4)

No significant change was found in the rate of DNA-synthesis in the 12 healthy, untreated controls during the period 1969 to 1971 (Table 5) The number of cpm was found to be increased when 2×10^6 cells were used compared to the number of cpm when 1×10^6 cells were used (Table 5)

The extent of thymidine incorporation using 2×10^6 cells was significantly higher in hyperthyroid patients from group A in the initial tests, i e before isotope therapy, than in euthyroid patients before surgery belonging to group B ($p<0\ 05$) or C ($p<0\ 05$), or in healthy controls ($p<0\ 05$) (Table 6)

Table 9

Incorporation of ^{14}C thymidine of lymphoid cells in vitro in presence of thyroglobulin before and after surgery for atoxic nodular goitre. The mean value for all 18 patients before therapy was 363 ± 129 cpm, when the individual values obtained in the absence of thyroglobulin are subtracted

Interval after surgery	No of pat	No of tests	Change in thymidine incorporation after surgery. No of cases		Mean of individual differences in thymidine incorporation cpm		Significance of the difference, p
			Increase	Decrease	Mean	SE	
6 weeks–3 months	13	13	10	3	322	277	NS
4–6 months	16	16	10	6	72	213	NS
7–12 months	14	22	6	8	86	255	NS
13–18 months	11	14	4	7	201	462	NS

Table 10

Healthy and euthyroid controls. Incorporation of ^{14}C thymidine by lymphoid cells in vitro with thyroglobulin added. The individual values obtained in the absence of thyroglobulin are subtracted

Year of test	Mean value cpm	SE	No of controls
1969/1970	196	168	12
1971	586	227	6

DNA-synthesis in the presence of thyroglobulin. In patients treated with ^{131}I for hyperthyroidism no significant changes were found in the DNA-synthesis when thyroglobulin was added as antigen compared with the pre-treatment values (Table 7). On the other hand, the DNA-synthesis in the presence of thyroglobulin in the groups treated by surgery was somewhat increased compared with the values before surgery, however, these differences were not statistically significant (Tables 8, 9). Similarly, the DNA-synthesis in the controls was slightly increased in 1971 compared to the period 1969/1970, but the differences were not statistically significant (Table 10).

Discussion

The results reveal that spontaneous DNA-synthesis in lymphocytes from patients with hyperthyroidism was higher than in lymphocytes from healthy controls, patients with atoxic goitre or hyperthyroid patients under treatment with antithyroid drugs. Furthermore, DNA-synthesis in the lymphocytes of hyperthyroid patients decreased after ^{131}I therapy.

The incorporation of thymidine by lymphoid cells in the presence of thyroglobulin was not affected by ^{131}I therapy for hyperthyroidism or by a reduction in the size

of the thyroid gland by surgery. These observations of thymidine incorporation in patients treated with ^{131}I for hyperthyroidism contradict previously published results (EINHORN et coll 1971) However, in this latter report, the effect of ^{131}I treatment upon the lymphocyte stimulation by thyroglobulin was calculated as the lymphocyte stimulation index (LSI), i e the ratio between the counts per minute obtained with and without thyroglobulin Since the spontaneous incorporation of thymidine by lymphocytes is decreased after ^{131}I therapy, the LSI will increase in the absence of any increased stimulation by thyroglobulin

The reason for the increased spontaneous DNA-synthesis in lymphocytes from hyperthyroid patients on the 4th day of culture as compared with lymphocytes from euthyroid individuals is not known

The spontaneous DNA-synthesis in cultured lymphocytes, sometimes also called background stimulation, is probably due to several different mechanisms Some of the cells are activated in vivo It is known from experiments that without the addition of antigen or polyclonal mitogens the rate of DNA-synthesis in lymphocytes cultured in vitro usually declines rather rapidly (HARRIS & LITTLETON 1966) However, on the 4th day of culture there certainly are some cells entering the proliferative phase that were initiated in vivo, possibly through the mediation of mitogenic factors generated in the culture Different components of the culture medium can be either mildly stimulatory or cytotoxic to lymphocytes The level of background activity is for example markedly dependent upon the serum used as supplement to the medium Macromolecules or antibodies to antigenic sites on the surface of lymphocytes are known to exert an influence on the background DNA-synthesis (LING 1968) The difference in the rate of this synthesis between lymphocytes from hyperthyroid and euthyroid individuals suggests, however, that thyroid hormones exercise some influence on DNA-synthesis This influence might be manifested directly through a stimulatory effect on lymphocytes or indirectly through an increase in the viability of cells cultured in vitro or by potentiation of some of the stimulatory mechanisms discussed

Another explanation of the increased DNA-synthesis seen in the lymphocytes from hyperthyroid patients is the possibility that in these patients a shift in the proportion of T- and B-lymphocytes with an increased frequency of T-cells occurs Although both T- and B-cells proliferate in response to antigens there is considerable evidence that in many situations DNA-synthesis in vitro is expressed primarily by the T-cells (GREAVES et coll 1974) However, the relative frequency of B- and T-cells in hyperthyroid patients does not seem to differ from that found in healthy individuals (LUNDELL et coll 1975)

Finally, it is also known that mononuclear phagocytic and adherent cells increase the proliferative response of lymphocytes to antigenic stimulation However, no absolute or proportional increase of such cells was observed in hyperthyroid patients (LUNDELL 1975)

Further investigations are obviously required to elucidate the mechanisms involved

in the increase of spontaneous DNA synthesis observed in lymphocytes from hyperthyroid patients In vitro experiments on the stimulatory capacity of thyroid hormones are in progress

The decrease in the spontaneous DNA synthesis which follows ^{131}I treatment of hyperthyroid patients is presumably due to the reduced level of thyroid hormones with subsequent repercussions on one or several of the possible mechanisms that are responsible for regulating the rate of lymphocytic DNA synthesis in these patients

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SUMMARY

The DNA synthesis of human lymphoid cells as estimated by the measurement of thymidine incorporation in vitro was investigated in healthy controls and in patients with various thyroid disorders before and after therapy Hyperthyroid patients treated with ^{131}I and surgery (euthyroid at initial blood sampling before surgery) patients with atoxic nodular goitre treated by surgery and healthy untreated control individuals comprised the material The synthesis of DNA in lymphocytes was higher in hyperthyroid patients in comparison with euthyroid individuals and decreased subsequent to ^{131}I therapy *in the hyperthyroid patients* No decrease was recorded in the other groups of patients No evidence suggesting a change in the lymphocyte reactivity to thyroglobulin was found in any of the patient groups.

ZUSAMMENFASSUNG

Die DNA Synthese menschlicher lymphoider Zellen gemessen mit der Inkorp...

... der Reaktivität der Lymphozyten gegenuber Thyroglobulin bei irgend einer der Patientgruppen wurde gefunden

RESUMÉ

La synthese de l ADN des cellules lymphoïdes h...

... des malades ayant un goitre

of the thyroid gland by surgery These observations *of thymidine incorporation in* patients treated with ^{131}I for hyperthyroidism contradict previously *published results* (EINHORN et coll 1971) However, in this latter report, the effect of ^{131}I treatment upon the lymphocyte stimulation by thyroglobulin was calculated as the lymphocyte stimulation index (LSI), i e the ratio between the counts per minute obtained with and *without thyroglobulin Since the spontaneous incorporation of thymidine by* lymphocytes is decreased after ^{131}I therapy, the LSI will increase in the absence of any increased stimulation by thyroglobulin

The reason for the increased spontaneous DNA-synthesis in lymphocytes from hyperthyroid patients on the 4th day of culture as compared with lymphocytes from euthyroid individuals is not known

The spontaneous DNA-synthesis in cultured lymphocytes, sometimes also called background stimulation, is probably *due to several different mechanisms Some of* the cells are activated in vivo It is known from experiments that without the addition of antigen or polyclonal mitogens the rate of DNA-synthesis in lymphocytes cultured in vitro usually declines rather rapidly (HARRIS & LITTLETON 1966) However, on the 4th day of culture there certainly are some cells entering the proliferative phase *that were initiated in vivo, possibly through the mediation of mitogenic factors* generated in the culture Different components of the culture medium can be either mildly stimulatory or cytotoxic to lymphocytes The level of background activity is for example markedly dependent upon the serum used as supplement to the medium Macromolecules or antibodies to antigenic sites on the surface of lymphocytes are known to exert an influence on the background *DNA-synthesis (LING 1968)* The difference in the rate of this synthesis between lymphocytes from hyperthyroid and euthyroid individuals suggests, however, that thyroid hormones exercise some influence on DNA-synthesis This influence might be manifested directly through a stimulatory effect on lymphocytes or indirectly through an increase in the viability of cells cultured in vitro or by potentiation of some of the stimulatory mechanisms discussed

Another explanation of the increased DNA synthesis seen in the lymphocytes from hyperthyroid patients is the possibility that in these patients a shift in the proportion of T- and B lymphocytes with an increased frequency of T-cells occurs Although both T- and B cells proliferate in response to antigens there is considerable evidence that in many situations DNA-synthesis in vitro is expressed primarily by the T cells (GREAVES et coll 1974) However the relative frequency of B and T cells in hyperthyroid patients does not seem to differ from that found in healthy individuals (LUNDELL et coll 1975)

Finally, it is also known that *mononuclear phagocytic and* adherent cells increase the proliferative response of lymphocytes to antigenic stimulation However, no absolute or proportional increase of such cells was observed in hyperthyroid patients (LUNDELL 1975)

Further investigations are obviously required to elucidate the mechanisms involved

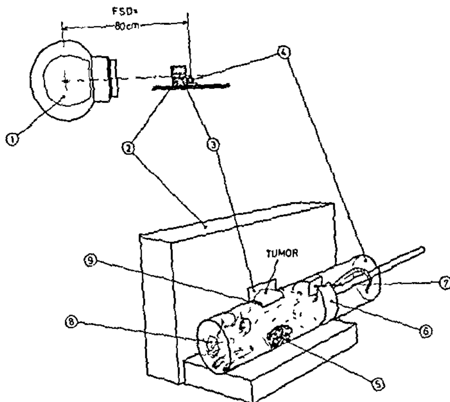


Fig 1 Set up for irradiation of tumor transplants in nude mice The mouse ...

... aperture (2)

The depth dose distribution for the 7 mm × 12 mm radiation field at FSD = 80 cm was determined from ionization chamber measurements in a tissue equivalent perspex phantom Measurements made with thermoluminescence discs (TLD 100 LiF, Ribbon, Harshaw) placed at the ionization maximum, varied within a few per cent of the corresponding ionization chamber readings of 105 rad/min The homogeneity of the dose distribution across the 7 mm × 12 mm radiation field was demonstrated by densitometer readings of exposed films The dose outside the radiation field was of the order of 0 5 per cent

Since the radiosensitivity of the skin of these animals is unknown, and furthermore,

The present work is also aimed at providing the necessary foundation for a full scale experiment on the time course of regression of human ovarian tumor transplants following a single, local exposure to ^{60}Co radiation

Material and Methods

Tumor pathology The tumor used (AN–LE) was a poorly differentiated adenocarcinoma of the ovary, taken at operation from a 55-year-old postmenopausal woman, suffering from ovarian cancer, stage IV She had received no previous therapy

Pathology and ultrastructure of this tumor are described fully in a report on the response to chemotherapy of AN–LE transplants in nude mice (DAVY & MOSSIGE, to be published)

Mice The animals were purchased from Gamle Bomholtgård, Denmark This nude strain is in the process of being backcrossed to a BALB/c/A/Bom background The animals are kept in a separate room at 27°C with automatically regulated 12 hour dark and light periods, under conventional, but very strict conditions Viability is variable and about half of the mice survive for several months

Implantation and measurement of tumor growth Tumor tissue from the operating theatre was transferred directly to the animal house where representative pieces were cut into small bits (ca 1 to 2 mm^3) and implanted subcutaneously on the dorsal surface of the mouse After a lag period of two months the implants began to grow Once a week the tumor cross-section of individual animals was measured by means of calibrated calipers

When the tumors had attained a cross-sectional area of about 75 mm^2, some of the animals were killed and their tumor tissue reexamined histologically AN–LE has been maintained in six passages to date Six female mice from the third passage were used in this preliminary investigation

Irradiation procedure, radiation quality and dosimetry The animals were not anaesthetized during irradiation, to avoid affecting the oxygen supply to, and hence the radiation response of, the tumor tissue

Thin-walled perspex mouse holders (4), were made (Fig 1) the internal diameter of which just allowed the mouse to enter A large hole (8) was made in the cranial end of the tube so the animal could breathe freely A piston arrangement in the 'tail'-end (6, 7) positioned the animal firmly in the holder By inserting a wad of cotton wool (5) in the holder just opposite the tumor, the latter was made to protrude through an opening in the tube (9), cut to fit the tumor region

A 5 000 Ci ^{60}Co therapy unit (TEM, Mobaltron 80) was used as radiation source (1) The tumors were irradiated at a focus-skin distance (FSD) of 80 cm and positioned

FROM THE RESEARCH INSTITUTE OF NATIONAL DEFENCE, S 172 04 SUNDBYBERG, SWEDEN

THE PATHOLOGY OF AMERICIUM 241

A NILSSON and AGNETA BROOMÉ-KARLSSON

Americium 241 is a transuranic element which has found use in industry On account of this and its metabolic behaviour and high energetic α irradiation ($\sim$5 45 MeV) it may present a considerable biologic hazard It is taken up mainly in the skeleton and the liver and also for long duration in the adrenal cortex, the ovary, the dental pulp as well as in the testes (HAMMARSTRÖM & NILSSON 1970) Americium is like plutonium a 'surface seeker in the skeleton but its initial uptake is however, about 1 4 times less than that of ^{239}Pu while the rate of loss from the skeleton is almost the same for the two nuclides (TAYLOR et coll 1969) Among various bones the concentration of ^{241}Am (ROSEN et coll 1972) varies within a factor of 4, that in the vertebrae being the highest and that in the small bones the lowest

LANGHAM & CARTER (1951) BENSTED et coll (1965) and TAYLOR & BENSTED (1969) have reported that ^{241}Am in doses of 63 to 2 5 μCi/kg has a large tumour spectrum including tumours of the bone, adrenal glands and haematopoietic tissues in rats Using doses between 25 and 2 5 μCi/kg to rats RUDNITSKAYA & MOSKALEV (1970) have also found tumours of the liver and degenerations in the liver, kidney, myocard and testes They also conclude that the irradiation of some endocrine organs particularly the pituitary and the thyroid may create a state of endocrine imbalance

A comparison between ^{239}Pu and ^{241}Am in rats have revealed that the former is a much more effective carcinogen than americium when the two nuclides are administered in approximately the same doses (BENSTED et coll)

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Human ovarian tumor transplants (AN–LE) are grown in the thymus defective nude mouse mutant (nu/nu BALB/c/A/Bom) Procedures for local irradiation of the tumors with ^{60}Co-radiation are described *An introductory test of the usefulness of these transplants in* studies of radiation effects on human tumors is performed by investigation of the time course of regression of AN–LE transplants in 6 mice, following single exposures to 375, 750, 1 180 and 1 575 rad, respectively

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Transplantate menschliche Ovarialtumoren (AN–LE) wurden in Thymus defizienten „nude" Maus Mutanten (nu/nu BALB/c/A/Bom) implantiert Die Methoden fur Lokal bestrahlung der Tumoren mit ^{60}Kobalt werden beschrieben In einem einfuhrenden Versuch wird der Nutzen dieser Transplantate fur Studien uber Strahleneffekte auf menschliche *Tumoren untersucht Dazu wird der zeitliche Verlauf der Regression von* AN–LE *Trans* plantaten in 6 Mäusen nach Einzelexponierung auf 375, 750, 1 180 oder 1 575 rad untersucht

RÉSUME

Des transplants de tumeur ovarienne humaine (AN–LE) se sont développés dans des souris mutantes nues à thymus anormal (nu/nu BALB/c/A/Bom) Les auteurs décrivent la technique d'irradiation locale des tumeurs avec le rayonnement du ^{60}Co Ils ont fait une expérimentation préliminaire concernant l'utilité de ces transplants pour l étude des effets des radiations sur les tumeurs humaines en étudiant l'évolution, en fonction du temps, de la régression des transplants AN–LE sur 6 souris après des expositions uniques à 375, 750, 1 180, et 1 575 rad respectivement

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ranging from a complete bone marrow aplasia to a slight hypoplasia In the lower dose groups, however, these changes were insignificant Usually all types of cells were depleted, the erythroid series, however, being most sensitive The majority of the marrows were loaded with fat and had heavily congested sinusoids In many aplastic marrows the sinusoids were besides completely destroyed leading to formation of large blood lakes In a few aplastic marrows an increase of reticular cells occurred with a slight intramedullar formation of argyrophilic and fuchsinophilic fibres By histologic methods it was also found that the effect of ^{241}Am was more severe in the vertebral marrow than in that of the long bones, whereas in the sternum the effect was intermediate In the long bones the injury was most marked in the distal end of the femur and in the proximal end of the humerus and tibia In the diaphyseal parts the lesion was less prominent and when regeneration occurred it was usually most evident here In the regenerative phase myeloid elements and megakaryocytes predominated, the erythroid elements being in many cases practically absent Thrombosis of the marrow occurred in a few per cent in all ^{241}Am groups, i e even the lowest ones

The spleen and other lymphatic tissues were persistently depleted of lymphatic cells (Table 2) and at the time of death the spleen was almost atrophic in most cases in the two highest dose groups A slight or moderate extra medullary haematopoiesis of all kinds, however, could still exist A considerable predomination of myeloid elements and megakaryocytes generally existed and in many mice there was also a heavy intramedullary and paraosteal proliferation of myeloid elements

Skeleton In the 16 μCi groups mice were killed with certain intervals (14 days, 1, 2 3 up to 9 months after administration of the nuclide) Some increase of the number of osteoblasts was found after 1 month in the distal metaphysis of the *femur* and after 2 months there was still some osteoblastic and osteoclastic activity Between 3 to 5 months the number of these cells decreased successively giving place to a sparse appearance of fusiform cellular elements which *increased in number* furthermore during month 8 to 9 At this time also a slight formation of fuchsinophilic fibres could be found Devitalized bone was abundant and at many sites it was being attacked by osteoclasts

In mice dying between 160 and about 250 days after injection of 16 and 8 μCi ^{241}Am/kg the bone tissue was generally heavily damaged Both in vertebrae and long bones the nucleated cells of the epiphyseal cartilage were few and in the metaphysis the trabeculae had more or less completely disappeared (Fig 1 a) The edge of the epiphyseal cartilage was quite even in correspondence with a complete disappearance of osteoclasts The thickness of the compact bone of the diaphysis was strongly reduced The endosteal cells, both osteoclasts and osteoblasts, had disappeared completely The osteocytes were shrunken and appeared pycnotic and their lacunae were conspicuously increased in size or empty (Fig 1 b) This could be observed everywhere but was most evident in the vertebral bodies Here the walls sometimes were

Table 1

Experimental design

Dose of ^{241}Am µCi/kg	Number of mice	Handling
16	25	One or two mice killed at certain intervals up to 9 months
16	40	Survivors
8	100	Survivors
0 4	50	Survivors
0 2	48	Survivors
0 04	51	Survivors
Control	50	Survivors

Most α-emitters, however, seem to be more effective cancerogens than nuclides emitting β-irradiation In the present report longevity, causes of death, dysplastic and dystrophic changes, carcinogenicity and the development of tumours induced by various doses of ^{241}Am are presented In some respects the late effects induced by the α-emitting ^{241}Am have been compared with those induced by the β-irradiation from ^{90}Sr described previously (NILSSON 1962, 1970)

Material and Methods

Totally 314 CBA male mice aged 75±5 days were injected intraperitoneally with ^{241}Am-citrate and 50 were used as untreated controls (*Table 1*) Before autopsy the animals were examined roentgenologically and the films were used as a guide for locating tumours From all mice i e both long time survivors and those killed at certain intervals by cervical dislocation, both femurs, tibias and humeri, the spine, the sternum and the head were fixed in Stieve's fluid and decalcified in 20 % formic acid for microscopy

The liver, kidney, testes, adrenals and spleen were weighed In addition to these organs also the lungs, the thyroid and the heart were fixed in Stieve's fluid Other tissues were fixed only when macroscopic lesions were found Conventional histologic methods were used, the sections routinely being stained according to the van Gieson method and with haematoxylin-eosin Occasionally Masson's trichrome method, Lillie's allochrome, the van Kossa method for calcium, azure eosinate, Einarson's gallocyanine, toloudine blue and congo red for amyloid, PAS by the method of Hotchkiss, Foot and Foot's silver method and Weigert s elastin were also applied

Results

Non malignant lesions

Haematopoietic tissues In almost all cases a moderate to severe effect on the haematopoietic and lymphatic systems was found in the two highest dose groups,



a



b

Fig 1 a) Femur, epiphyseal region, mouse 364 days after injection of 8 μCi ^{241}Am-citrate kg body weight The compact bone and epiphyseal cartilage almost completely destroyed Heavy periosteal reaction van Gieson ×100

most frequent in the vertebrae They were, however, not particularly conspicuous and did never predominate over the destructive lesions

The first microscopic osteosarcoma was detected in the 16 μCi group after 231 days in the proximal epiphysis of the tibia and after 280 days in the wing of the first sacral vertebrae of the 8 μCi group As a rule these processes started inside Howship's lacunae or in narrow tunnels in the bone Most tumours appeared as small buds in the angel between compact bone and the epiphyseal cartilage in the vertebrae and in the epiphyseal part of the long bones

In the 0 4, 0 2 and 0 04 μCi groups the abnormalities found in the skeleton at high

Table 2

Mean weights

Dose of ^{241}Am µCi/kg	Number of mice	Weight of Mice x±SE g	Liver x±SE g	Spleen x±SE mg	Testes x±SE mg	Adrenal x±SE mg	Survival days
16	39	14.1±0.28	—	30.3±3.8	23.1±1.4*	—	174.9±9.5
8	100	17.8±0.39	0.7289±0.0963	33.7±3.2	57.5±1.6**	4.6±0.10	301.8±6.5
0.4	50	21.3±0.20	2.4829±0.0731	85.9±7.6	45.0±2.0	7.0±0.85	684.9±18.2
0.2	48	22.1±0.90	2.5796±0.2556	76.1±5.4	47.2±3.6	5.6±0.22	697.8±25.8
0.04	51	22.7±0.94	2.6710±0.273	76.8±1.2	49.4±3.1	5.7±0.22	731.7±17.6
Control	50	20.8±0.76	1.9467±0.0187	93.1±7.5	49.2±3.9	5.8±0.44	779.7±17.4

Appendix

Absolute and relative weight of testes, liver, spleen and adrenals for five normal serially killed mice

	Days	Absolute weight (mg)	Relative to body weight (per cent)
* *Testes, killed at*	*180*	*131.4±4.0*	*0.37*
** Testes, killed at	300	141.9±3.2	0.35
Liver, *killed at*	*180*	*1.2647±0.0665*	*5.3*
	300	1.4663±0.0339	4.8
	570	*1,7709±0.0778*	*5.3*
Spleen, killed at	180	65.2±1.7	0.18
	300	*75.1±3.2*	0.19
	570	86.2±8.9	0.26
Adrenal, killed at	*180*	*2.9±0.13*	0.008
	300	3.7±0.10	0.009
	570	3.3±0.06	0.010

extremely thin and the structure was kept together only by the periosteal tissue. Complete fractures of the vertebral body without reaction or only a slight attempt to formation of a callus could be detected. This destruction of the bone was obviously a process of osteolysis and necrosis since osteoclastic activity was with some exceptions insignificant. Up to about 240 to 280 days in the 8 µCi/kg group the microscopy of the bone tissue was totally dominated by this destructive phase generally without any capacity for repair reactions. At this time osteoclasts started to appear, destroying circumscribed necrotic tissues or more diffusely distributed devitalized bone. In many bones the epiphyseal cartilage was almost completely absent. The surrounding of the nutritional foramen was also often attacked and the foramen significantly widened. Around 280 days after the injection of 8 µCi ^{241}Am/kg the first evident signs of repair could be detected mostly in lacunar areas with osteoclastic activity (Fig. 2 a). These cells were fusiform or sometimes osteoblastlike elements with the ability to osteoid formation (Fig. 2 b). Such areas of reparation were usually

Liver A slight periportal fibrosis was a common finding in a majority of the livers given 8 μCi Parenchymal changes varying from a slight pleomorphism of the liver cell nuclei to an extensive probably hypoxemic fatty degeneration and occurrence of multiple focal necrosis were also observed in numerous cases In some livers the number of binucleate cells and the degree of nuclear pleomorphism appeared abnormally high in the 16 to 8 μCi groups In a significant number of livers the epithelial cells of the biliary canalicule appeared to be swollen and in a few livers heavy multifocal proliferations of these structures occurred (Fig 3) In a few cases numerous microabscesses also existed

In the 0 4, 0 2 and 0 04 μCi groups and in the control groups dystrophic changes of various types such as fatty degenerations, necrosis and microabscesses appeared approximately with the same frequency

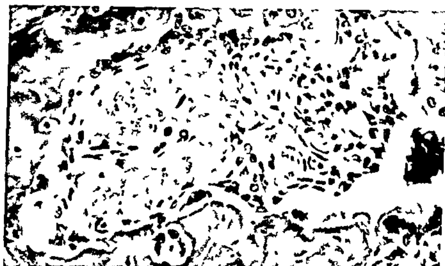
Adrenal glands The weight of the adrenals was in many mice in the 8 μCi group higher than normally In Table 2 it is also evident that the mean weight for the whole group of animals was significantly increased as compared to that of normal mice of the same age In some cases the reason for the increased weight seemed to be a hyperplasia of the cortex sometimes evidenced by small nodular cortical hyperplasia In some cases extracapsular hyperplasia nodules were encountered

In mice of advanced age the weight of the adrenal glands continued to rise The mean weight of the adrenals for mice 685 to 732 days old in groups 0 4, 0 2 and 0 04 and the control mice (780 days) were thus statistically significantly increased over that of mice of 300 and 570 days of age (Table 2 and appendix) No such difference however, existed between the low dose groups and their controls which means that the adrenals are increasing in weight with age One reason for the increased weight of the adrenal in mice of old age seemed to be related to varying degree of hyperplasia of the adrenal medulla and at the same time an atrophy of the cortex This hyperplasia which sometimes was difficult to separate from a tumour (phaeochromocytoma) was generally more frequent and marked in *the 0 4 μCi group than in* the controls (Fig 4) In most cases with medullary hyperplasia a more or less conspicuous destruction of Zona reticularis and a narrowing and atrophy of Zona fasciculata with a dilatation of *its sinusoids* appeared In many cases the neurons of the medulla appeared greatly increased in size and had a large prominent nucleus. Sometimes the hyperplastic medulla was in direct contact with the adrenal capsula

Kidney In the 16 μCi group only *serially sectioned mice* were examined microscopically Lesions, usually focally situated, were found 6 months after th[illegible]
of ^{241}Am [illegible]
and in a [illegible]
were hy[illegible] and the epithelium almost occluded the lumen A slight interstitial focal fibrosis was also observed as well as a *few hyaline* casts



a



b

f 8 C kg 241Am
tion by

b) Thoracic vertebra mouse 313 days after inject on of 8 μCi/kg ^{241}Am La cunae with a few osteoclasts and a heavy proliferation of osteoblast l ke cells and apposition of immature bone van Gieson ×250

age such as devitalization and osteoporosis were usually more developed than the age related lesions in the control group In the control animals the cortical bone particularly in the femur generally grew thinner with advancing age or could be built up by a number of thin bone spiculae separating large lacunae In some cases there was also a strong formation of endosteal bone

Table 3

Kidney lesions Percentage in relation to dose

Type of lesion	Dose of ^{241}Am μCi kg			Control
	0 4	0 2	0 04	
I	30 9	24 3	10 3	37 0
II	35 7	13 5	46 3	37 0
III	30 9	51 4	28 2	22.2
IV	2 4	2 7	2 6	3 7
V	—	8 1	10 3	—

nective tissue was increased Lesions of this type were not found in control material of comparable age

In the 8 μCi group practically all mice had lesions of the kidney varying from a slight to a relatively strong interstitial peri- and intraglomerular fibrosis In some cases the glomerular tufts were sclerotic The tubuli were often dilatated and could have an atrophic epithelium

In the three lowest dose groups 0 4, 0 2, 0 04 and in the control material practically all kidneys had pathologic changes of the same type and frequency The glomeruli were as a rule more heavily affected than the interstitial tissue The lesions were approximately divided into different groups (Table 3) In the first group (I) the glomeruli capsule was thickened and hyalinized and the epithelium transformed to a stratified usually single-layered epithelium or absent The glomerular tufts were usually slightly hyalinized and slightly fibrotic In the second group (II) the abnormalities were more aggravated and besides those mentioned in group I there was also a considerable fibrosis of the Bowman capsule and periglomerularily (Fig 5 b) In the third group (III) there was in addition a heavy interstitial fibrosis which in some cases could involve the whole organ In a few cases (group IV) a chronic pyelonephritis was found The fifth group (V) consisted of kidneys with only minor changes such as a more or less evident dilatation of the tubuli or the glomeruli

Testis As compared to the normal group there was an accelerated relative and absolute testicular weight loss in the ^{241}Am treated mice (Table 2) In most testes from mice in the higher dose groups there was aspermia or a marked hypospermia and tubular degeneration In older mice a slight interstitial fibrosis and a concomitant reduction of Leydig s cells occurred

A congestion was macroscopically detectable of the superficial testicular vessels in numerous testes Microscopically there was a necrosis of the vessels which, however, stained intensely blue with H-E or black with the van Kossa method on account of calcium deposits (Fig 6 a) In the 8 μCi group 81 per cent of the mice had these lesions The mean survival for these mice was 302 days Similar abnormalities



Fig 3 Liver mouse 191 days after injection of 8 / Ci [241] Am/kg Proliferation of biliary canaliculi Atypic and pleomorphic hepatocyte nuclei van Gieson ×250

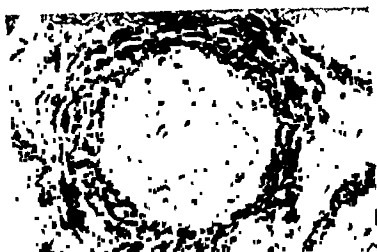


Fig 4 Hyperplasia of the adrenal medulla mouse 553 days after 0 4 / Ci [241] Am/kg Weight of the glands 9 6 mg H E ×250

With increasing age these changes grew progressively worse within focal areas Thus after 9 months the lesions were conspicuous with numerous hyaline casts in the tubuli or inside the Bowman capsule Locally the glomeruli were slightly to moderately fibrotic and in many cases contracted In these areas the interstitial con



a



b

Fig. 6 Testis mouse a) Vascular dystrophically calcified necrosis 289 days after injection of 8 μCi/kg ^{241}Am.

b) 659 days after injection of 0.2 μCi ^{241}Am/kg Proliferation of the intimal layer and partly occlusion of the vascular lumen Considerable perivascular fibrosis Lillie's allochrome × 400

were found also in the three lowest dose groups (0.4 0.2 0.04) and in the control material and were 73 per cent (survival time 658 days) 53 per cent (survival time 731 days) 56 per cent (survival time 708 days) and 93 per cent (survival time 769 days) respectively In the lowest dose group the first lesions appeared after 452 (0.4) 473 (0.2) and 473 days (0.04) respectively and in the control group after 580 days In the 8 μCi group the first case was found after 165 days



a



b

b) Untreated control mouse 675 days after start of exper ment Hyalinization of the Bowman capsule Slight fibrosis of the capsule and its surrounding hyaline casts d lated tubuli with degenerated epithel um Cellular prolifera tion within the glomerular capsule *Lill e s allochrome* × *400*

Table 5

Anatomic distribution of ^{241}Am induced hard tissue tumours

Site	Number of tumours in relation to dose of ^{241}Am/kg				
	16 n 39	8 n 100	0 4 n 50	0 2 n 48	0 04 n 51
Long bones					
Femur	2	3			
Tibia	1	1			
Humerus		1			
Radius		2			
Total	3	7			
Spine					
Cervical		1			
Thoracic		14			
Lumbar	1	16		1	1
Sacral		3	1*		
Coccygeal				1**	
Total	1	34			
Others					
Pelvic bones*		1			
Sternum		1			
Head		2	1*		
Total	4	45	2	2	1

* These bones were not sectioned routinely
Osteomas
** Chondroma
n number of mice

In a fe ...
an ...
as ... radiation

Malignant lesions

The number and induction time of various types of neoplasia appear in Table 4

Tumours of the hard tissues In the 16 μCi group a total of four microscop...
blas...

...osteosarcomas were of osteoblastic type with a moderate bone formation In some tumours an abundancy of osteoclasts was found In the 0 4 μCi group two microscopic tumours with morphologic characteristics of osteomas appeared The two tumours found in the two lowest dose groups were microscopically osteosarcomas

Anatomic localization The site of the bone tumours is indicated in Table 5 The

Table 4

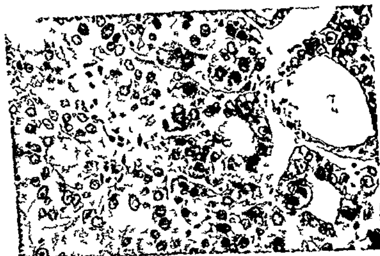
Number and induction time (days) of tumours in relation to dose of ^{241}Am

Tumours of	Dose of ^{241}Am μCi/kg											
	16 n 39		8 n 100		0 4 n 50		0 2 n 48		0 04 n 51		Control n 50	
	No	Induction	No	Induction	No	Induction	No	Induction	No	Induction	No	Induction
Bone	4	254 0	45	352 5 ±9 1	2	708	1	783	1	785	0	
Liver					36	665 ±19	32	678 ±22	34	708 ±23	28	731 ±24
Lung			1	280	5	746 ±51 6	12	730 ±45 5	15	828 ±31 8	12	789 ±31 5
Lympho-reticular system			10	278 ±25 8	3	746			3	742	2	608
Vessel					1	779			1	847	1	964
Adrenal glands					1	452						
Kidney							1	834				
Orbit									1	847		
Coccyx (Chondroma)							1	888				

Besides these lesions of medium sized arteries, proliferation of the endothelium was found in numerous smaller arteries, generally combined with a heavy proliferation of the adventitial layer (Fig 6 b)

Myocardium The lesions of the myocardium mainly found in the 8 μCi group were characterized by multifocal occurrence of degeneration and necrosis with occasional signs of alterative inflammations of the myocardial tissues Numerous necrosis were dystrophically calcified In the other groups one case of myocardial degeneration was found in each of the 0 4 and 0 2 μCi groups In the control group no such lesions appeared

Other tissues The vertebral discs, particularly those between the 3rd and 4th sacral vertebrae and those between the 4th sacral vertebra and the first and second coccygeal vertebrae, were strongly increased in size and had a tendency to protrude bilaterally No such lesions appeared in the two highest dose groups but they were common in the lowest dose groups (0 4, 0 2, 0 04) and in the control material, being 71 4, 64 6, 69 6 and 44 0 per cent, respectively However, mice having these lesions were of a high mean age, being 763 ± 25 8, 789 ± 20 4, 773 ± 24 8 and 731 ± 15 6 days for the control material and the 0 04, 0 2 and 0 4 μCi groups, respectively



a



b

Fig 7 a) L e ma gnant hepatoma, (hepatocellular carc noma) mouse 665 days af er n ect on of 0 2 μC kg^{-1} Am H E 250

b) Lung w h me astases of mal gnant hepatoma. Same an mal as n F g. 6 a. H E 100

of the frequency of the lung tumours Thus no tumours were found in the 16 μCi group and only one in the 8 μCi group whereas a considerable number occurred in the older m ce of the lowest dose groups and the control material All tumours were alveolar cell carc nomas (Fig 8) in one case combined with lung adenomatos s (Table 7) They occurred e ther as solitary or multiple tumours The sol tary tumours

Table 6

Hepatomas

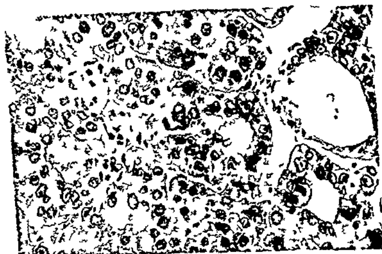
Dose of ^{241}Am μCi/kg	Number of mice	Number of hepatomas	Frequency (per cent)	'Induction time' Days ± SE	Weight of liver x ± SE	Relative weight, liver x ± SE	Number and frequency of hepatomas with metastases (per cent)	
0 4	50	36	72	665 ± 19	3 051 ± 0 238	13 7 ± 0 92	2	5 6
0 2	48	32	67	678 ± 22	3 192 ± 0 092	14 6 ± 1 01	4	12 5
0 04	51	34	67	708 ± 23	3 346 ± 0 072	14 4 ± 0 77	3	8 8
Control	50	28	56	731 ± 24	2 269 ± 0 167	10 3 ± 0 64	6	21 4

two osteomas in the 0 4 μCi group were located in the skull and in a lumbar vertebrae, respectively The chondroma was found in the first coccygeal vertebra

Liver tumours The frequency, induction time and other data of the liver tumours are recorded in Table 6 In the two highest dose groups no liver tumours were observed In the 0 4, 0 2 and 0 04 groups of mice as compared to controls there seems to be a general trend to a shortened tumour induction time For the groups this difference is at the 95 per cent interval The frequency of liver tumours is also slightly higher in the ^{241}Am treated mice, though not statistically separated from the control material As regards the weight of the livers both the absolute ($p < 0\ 01$) and the relative weights ($p < 0\ 001$) are statistically increased over those of the controls The tumours were of hepatocellular type and were classified as hepatomas according to the EULEP nomenclature Metastasing hepatomas have been classified as malignant hepatomas (Fig 7 a) Metastases were usually multiple and restricted to the lungs (Fig 7 b) and thoracic wall and in some cases also to the kidneys

Lymphoreticular tumours Ten lymphosarcomas were found in the 8 μCi group They were of lymphatic and non-thymic type A varying infiltration of lymphoid cells usually appeared in the tissues surrounding the lumbar and thoracic vertebrae The mean latency time (Table 4) was 278 ± 26 days In the 0 4 μCi group three lymphosarcomas appeared after 660, 714 and 863 days, respectively Two of these were restricted to the mesenteric lymph node and one to the spleen In the 3 cases in the 0 04 μCi group the thymus, spleen and lymph glands, but not the marrow, were involved in all cases Around the thoracic vertebrae a 'lymphoma' also appeared in one case The induction times were 691, 749 and 785 days, respectively The two cases of lymphosarcomas in the control group appeared after 594 and 621 days, respectively and mainly affected the mesenteric lymph node

Lung tumours In Table 4 the number and induction time of the lung tumours are recorded Generally the age of the animals and not the dose of ^{241}Am was decisive



a



b

Fig 7 a) L er mal gnant hepatoma, (hepa ocellular carcinoma) mouse 665 days af er nject on of 0 2 μC kg Am H E 250

b) Lung w th metastases of mal gnant hepatoma Same an mal as in F g. 6 a H E 100

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Table 6

Hepatomas

Dose of ^{241}Am μCi/kg	Number of mice	Number of hepatomas	Frequency (per cent)	'Induction time' Days $\pm$SE	Weight of liver x$\pm$SE	Relative weight, liver x$\pm$SE	Number and frequency of hepatomas with metastases (per cent)	
0 4	50	36	72	665$\pm$19	3 051$\pm$0 238	13 7$\pm$0 92	2	5 6
0 2	48	32	67	678$\pm$22	3 192$\pm$0 092	14 6$\pm$1 01	4	12 5
0 04	51	34	67	708$\pm$23	3 346$\pm$0 072	14 4$\pm$0 77	3	8 8
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Lung tumours In Table 4 the number and induction time of the lung tumours are recorded Generally the age of the animals and not the dose of ^{241}Am was decisive

Table 8

Causes of death

Diagnoses	^{241}Am μCi/kg body weight					Control
	16	8	0.4	0.2	0.04	
Bone marrow aplasia	5 (276±7)	10 (306±9)	—	—	—	—
Bone marrow aplasia in combination with						
Liver degeneration	—	9	—	—	—	—
Myocardial degeneration	—	5	—	—	—	—
Haemorrhagic diathesis and liver degeneration	—	3	—	—	—	—
Intestinal haemorrhagic inanition	26 (134±6)	4 (287)	—	—	—	—
Inanition	8 (207±20)	20 (313±12)	3 (807)	1	1	11 (800±16)
Liver degeneration	—	6	1	2	3	1
Lympho-reticular tumours	—	10 (278±26)	3 (746)	—	3 (742)	2 (608)
Osteosarcomas	—	7 (352±15)	—	—	—	—
Hepatomas	—	—	24 (661±22)	21 (698±25)	26 (687±29)	17 (718+32)
Alveolar cell carcinomas	—	1	4	7	7	6
Adrenal cortical carcinoma	—	—	1	—	—	—
Infections	—	2*	4***	3****	3*****	2**
Other diagnoses	—	2		2	1	1
Not stated (at autopsy)	—	19	6	7	6	7
Not stated (postmortal autolysis)	—	2	4	5	1	3
Total	39	100	50	48	51	50

Days ± SE within parenthesis

* One acute purulent bronchopneumonia. One fibrino purulent peritonitis

** One chronic pyelonephritis. One acute purulent vesiculitis with peritonitis

*** Two purulent panophthalmitis. One purulent peritonitis. One chronic pyelonephritis

**** One acute purulent bronchopneumonia. One multiple abscesses in the head. One chronic pyelonephritis and multiple abscesses in the head

***** One purulent pneumonia. One chronic pyelonephritis. One chronic glomerulonephritis

μCi group. In the 0.04 μCi group a tumour was also found in the orbital tissue but could not be identified due to post-mortal autolysis.

In the 0.4 μCi group one cortical carcinoma was found. There was also a considerable ... [illegible] ...per- ... 4)

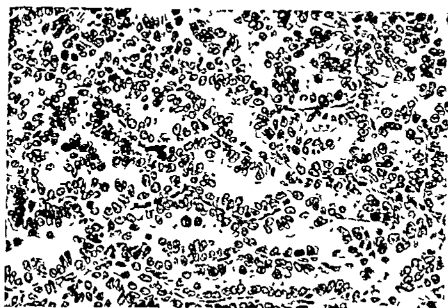


Fig 8 Alveolar cell carcinoma, mouse 610 days after injection of 0 1 μCi/kg ²⁴¹Am H-E ×250

could reach a considerable size (hazel-nut or larger) and were in these cases the only cause of the death of the animal The tumours were highly malignant with a considerable ability to spread inside the pleural cavity or to metastasize to other tissues In one case metastases were found in both adrenals, in one kidney and in the liver

Other tumours Three tumours of the vessels were detected Two of those which were found in the 0 4 and 0 04 μCi group, respectively, were cavernous haemangiomas of the subcutaneous tissue and the other in the control material was an angiosarcoma involving the sternal and vertebral marrows and surrounding paravertebral tissues and the spleen One cortical carcinoma of the kidney was found in the 0 2

Table 7

Lung tumours

Dose of ^{241}Am μCi/kg	Number of alveolar cell carcinomas	Induction time Days + SE	Percentage
16		—	—
8	1	280	1
0 4	5	746 ± 51 7	8
0 2	11	730 ± 45 4	25
0 04	15	828 ± 31 9	29
Control	12	789 + 31 5	24

Table 8

Causes of death

Diagnoses	^{241}Am / µCi/kg body weight					Control
	16	8	0.4	0.2	0.04	
Bone marrow aplasia	5 (276 + 7)	10 (306 + 9)	—	—	—	—
Bone marrow aplasia in combination with						
Liver degeneration	—	9	—	—	—	—
Myocardial degeneration	—	5	—	—	—	—
Haemorrhagic diathesis and liver degeneration	—	3	—	—	—	—
Intestinal haemorrhagic nanition	26 (134 + 6)	4 (?87)	—	—	—	—
Inanition	8 (?07 + 20)	20 (313 + 12)	3 (807)	1	1	11 (800 + 16)
Liver degeneration	—	6	1	2	3	1
Lympho-reticular tumours	—	10 (278 + ?6)	3 (746)	—	3 (74?)	2 (609)
Osteosarcomas	—	7 (35? + 15)	—	—	—	—
Hepatomas	—	—	24 (661 2?)	21 (698 + 25)	26 (65? 29)	17 (718 + 3?)
Alveolar cell carcinomas		1	4	7	7	6
Adrenal cortical carcinoma	—	—	1	—	—	—
Infections	—	2*	4***	3****	3*****	2**
Other diagnoses	—	2		2	1	1
Not stated (at autopsy)		19	6	7	6	7
Not stated (postmortal autolysis)	—	2	4	5	1	3
Total	39	100	50	48	51	50

Days SE within parentheses

* One acute purulent bronchopneumonia. One fibrino purulent peritonitis

** One chronic pyelonephritis. One acute purulent vesiculitis with peritonitis

*** Two purulent panophthalmitis. One purulent peritonitis. One chronic pyelonephritis

**** One acute purulent bronchopneumonia. One multiple abscesses in the head. One chronic pyelonephritis and multiple abscesses in the head

***** One purulent pneumonia. One chronic pyelonephritis. One chronic glomerulonephritis

µCi group In the 0.04 µCi group a tumour was also found in the orbital tissue but could not be identified due to post mortal autolysis

In the 0.4 µCi group one cortical carcinoma was found. There was also a considerable hyperplasia of the adrenal medulla. It was, however, not possible to determine whether these lesions were true tumours (phaeochromocytomas) or not (Fig. 4)

Causes of death From Table 8 it is evident that in the two highest dose groups the most probable cause of death was, directly or indirectly, associated with a disturbance of the haematopoietic system The disturbed haematopoiesis was also in many cases combined with other lesions as well (Table 8) Thus, the haemorrhages of the gut were probably related to an enteritis of the haemorrhagic type

At autopsy the cause of death could not be stated in 19 mice belonging to the 8 μCi group All these mice had a bone marrow hypoplasia which, however, was insufficiently severe to explain the death

Each of the 7 mice dying from osteosarcoma in the 8 μCi group had all more than one tumour out of which at least one was of macroscopic extent

In the degenerated livers multiple necroses and a severe wide-spread fatty degeneration, hyperemia and ectatic vessels existed

In two cases (in the 8 μCi group) spontaneous fractures of the vertebral bodies complicated with a compression of the spinal cord may be a probable cause of death (Table 8, 'other diagnoses') Within the low level groups and between these and the control group no significant differences as regards the cause of death existed In all the groups the majority of the mice died with hepatomas The frequency was approximately the same, being 48, 44, 51 and 34 per cent in the 0 4, 0 2 and 0 04 μCi groups and the controls, respectively It should, however, be pointed out that many of the hepatomas occurred together with a severe chronic glomerulonephritis

The adrenal tumours detected in the 0 4 μCi group after 452 days had a weight of 31 7 mg The tumour had ruptured and caused a severe bleeding to the peritoneal cavity Under the heading 'other diagnoses' (Table 8) a carcinoma of the kidney and an angiosarcoma were found in the 0 2 μCi groups, respectively In the 0 04 μCi group one mouse had mesenteric disease and one a tumour of the eye

Discussion

In the present investigation doses of 16 and 8 μCi ^{241}Am/kg induced a bone tumour incidence of 7 7 and 27 per cent, respectively In the two lowest dose levels of 0 2 and 0 04 μCi/kg tumours also appeared, but in a low frequency (2 %) In rats TAYLOR et coll found an incidence of 47 per cent after a dose of 7 0 μCi ^{241}Am/kg and BENSTED et coll 21 per cent after a dose of 2 5 μCi ^{241}Am/kg

It is interesting to compare the carcinogenicity of ^{90}Sr with that of ^{241}Am ^{90}Sr doses between 1 000 and 800/μCi kg seem to give an optimum bone tumour incidence of about 90 to 95 per cent whereas a dose of 200 μCi/kg gives an approximate tumour incidence of about 35 per cent and 50 μCi/kg about 6 per cent Even if it could be anticipated that lower ^{90}Sr doses could produce bone tumours, ^{241}Am therefore seems to be a more effective carcinogen than ^{90}Sr since it can induce tumours at significantly lower dose levels On the other hand, the frequency of tumours induced by ^{241}Am does not seem to be so high as that induced by optimum doses of ^{90}Sr Multiple tumours (2 to 3 or even more) in individual animals are frequent in ^{90}Sr

reated mice at optimum doses This, however, does not seem to be the case after ^{241}Am administration The reason for this might be difficult to explain but may be associated with factors such as survival times, volume of bone tissue irradiated, ocalization and destructive effect in the body

In the present investigation the bone destruction was in general more marked and reparative processes less evident after doses of 8 and 16 μCi ^{241}Am/kg than after 700 to 800 μCi ^{90}Sr/kg which may indicate that the Am dose levels were superoptimum and leading to an 'over kill' of cells This is important since reparation and the ability to tissue proliferation seems to be a necessary prerequisite for tumour induction ^{90}Sr tumours like ^{241}Am tumours also emanate from structures inside the bone Those induced by ^{90}Sr usually starts either from osteoblastlike cells along the endosteal linings as small bone producing buds or just below the epiphyseal cartilage in the diaphysis They may, however, also arise like islands inside the bone marrow from multipotent reticular cells with the ability to form osteoid The ^{241}Am tumours on the other hand were preferably found in immediate contact with the epiphyseal cartilage or very often in lacunar areas of compact bone in close vicinity to the epiphyseal cartilage and not in the diaphyseal part It is also notable that the majority of the ^{241}Am tumours were found in the vertebrae, whereas after optimum ^{90}Sr doses the long tubular bones are the most frequent site of osteosarcomas At superoptimum ^{90}Sr doses the spine is, however, the most frequent site of tumour induction whereas at low doses there is a predomination in the diaphyses of the long bones (NILSSON 1970)

Most ^{90}Sr induced tumours arising from endosteal linings are of osteoblastic type whereas those emanating as islands in the bone marrow are predominantly of fibroblastic type After high and optimum doses osteoblastic osteosarcomas predominate, whereas lower doses give an increased incidence of fibroblastic osteosarcomas (NILSSON 1970) The ^{241}Am tumours on the other hand were all of osteoblastic type

Using doses of ^{90}Sr between 800 and 400 μCi/kg angiosarcomas of the bone marrow do appear with an incidence of about 2 and 4 5 per cent, respectively With ^{241}Am no tumours of this type were found in the bone marrow in spite of the fact that the bone marrow was usually heavily injured in the proximal and distal parts of the long bones This difference may be associated with the fact that the β rays of ^{90}Sr and ^{90}Y has a much longer range exposing larger volumes of the bone marrow to a cross fire It should also be pointed out that the lesion of the bone marrow after administration of ^{241}Am differed from that of ^{90}Sr With ^{90}Sr the lesions usually are located proximally and distally in the long bones during the first few months after the administration of the nuclide, whereas later on these parts regenerate and the marrow of the diaphysis atrophies After injection of ^{241}Am the lesions in the diaphysis were never prominent

With the high doses of ^{90}Sr (1 600 μCi/kg) carcinomas of the mucous membranes of the head in close vicinity of the bone, are induced in a high frequency (NILSSON

1968) This was not the case with ^{241}Am with the doses employed With ^{241}Am as with ^{90}Sr lymphosarcomas are induced With high doses of ^{90}Sr a fairly high number of these emanates from the thymus whereas with lower doses the majority seem to arise mainly in the bone marrow (NILSSON 1971) All the lymphosarcomas induced by the 8 μCi ^{241}Am were generalized lymphosarcomas of short induction time (278 $\pm$ 25 8 days) and probably originating from the bone marrow The lymphosarcomas found in the lower dose groups and in the control group were not detected until after 600 to 700 days They were usually restricted to a lymph node and were not generalized Furthermore the frequency of the low dose lymphosarcomas did not differ from that of the control material

As regards lesions in the soft tissues ^{241}Am is as a consequence of its widespread localization much more destructive than ^{90}Sr In the testis the lesions induced by ^{241}Am are largely irreversible and progressive ^{90}Sr on the other hand produces heavy abnormalities initially but they regenerate after about 2 months following administration of the nuclide In the two highest dose groups ^{241}Am had a highly destructive effect of the seminiferous epithelium whereas such an effect in the lower doses is questionable Whether or not ^{241}Am could influence upon the development of the vascular lesions found is difficult to prove It might, however, be anticipated that the nuclide can accelerate the rate of development of these lesions Thus not less than 81 per cent of the testes had vascular lesions in the 8 μCi/kg group at a mean age of 301 days whereas the first case with such lesions in the control group—though reaching 93 per cent—were not found until 580 days after the start of the experiment In the 8 μCi group the first lesion was found already after 165 days In the lower dose groups the tendency to an earlier appearance persists The explanation for this might hypothetically be associated with a general effect of the physical health of the ^{241}Am-treated animals ^{241}Am also induces lesions in the liver and adrenals, which, however, does not seem to be the case with ^{90}Sr

In the two highest ^{241}Am groups liver tumours did not appear The only reason for this seems to be the great reduction of the survival time In the CBA strain the frequency of liver tumours is very high in males but the tumours do not start to occur until the mice have reached an age of about 450 days In the low dose groups of the present material the frequency of these tumours is somewhat, although not significantly higher than in the control material (Table 6) On the other hand the shortened latency time and the increased liver weight of the ^{241}Am-treated animals seem to confirm the general opinion that radiation may accelerate tumour formation in animals with a high normal incidence of tumours

In a previous report (HAMMARSTROM & NILSSON) it has been stated that ^{241}Am accumulates strongly and for a long time mostly in the zona glomerulosa of the adrenals Others (BENSTED et coll , TAYLOR et coll) have found cortical tumours in rats The low incidence of adrenal tumours found in the present investigation is therefore most likely associated with the fact that the dose levels employed were not optimum for induction of cortical tumours ^{241}Am in the doses employed do

not seem to influence the incidence of lung tumours which also seems to be the case for the other soft tissue tumours found

^{90}Sr even in high doses does not seem to induce kidney lesions In the present material the findings indicate a nephrotoxicity for the two highest ^{241}Am doses as evidenced by the early appearing fibrosis in mainly the cortical parenchyma No such lesions were found among control mice of comparable age The kidney lesions found in the low dose groups of mice and in the control material were on the other hand all of about the same type and frequency, including chronic glomerular nephritis with hyalinization of the glomerular capsule, productive inflammation, degeneration of tubular epithelium and a high frequency of hyaline casts In the low dose range ^{241}Am therefore does not seem to have any significance for the development of the lesions found

As regards the non malignant lesions it is obvious that ^{241}Am had a very destructive effect of the bone marrow which developed aplasia or hypoplasia with destruction of the sinusoidal system and formation of a fatty marrow In many cases also thrombosis of the vascular system occurred and a more or less evident fibrosis Generally the spleen was also heavily injured contrary to what is found after ^{90}Sr-administration This explains the numerous cases of death from haematopoietic insufficiency and related findings such as hypoxemic degeneration of the liver, myocardial necrosis and evidence of haemorrhagic diathesis The haemorrhages in the intestine might also be related to the haematopoietic disorder with or without complication with terminal bacterial infections The high frequency of inanition like the increased frequency of infection such as pneumonia, purulent vesiculitis, peritonitis, purulent inflammations of the orbital tissues and in the paradental tissues etc is probably also related to the impaired haematopoietic condition and an incapacitation of the immunological system

SUMMARY

Male CBA mice were injected intraperitoneally with different doses of ^{241}Am-citrate (16, 8 0 4 0 2 0 04 μCi/kg) The two highest doses were highly destructive of the haematopoietic tissues testes and bone tissue The highest frequency of induced tumours of the skeleton and haematopoietic tissue was found in the 8 μCi group In the liver, adrenal glands, kidney and heart degenerative lesions were found mainly in the higher dose groups In the lower dose groups degenerative lesions seemed to appear earlier and at a higher frequency than in the control group

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po[illegible] ...eugewebe hochgradig destruktiv Die hochste Frequenz an induzierten Tumoren des Skeletts und des hämatopoietischen Gewebes fand sich bei der 8 μCi Gruppe Vorzuglich bei den hoheren Dosis Gruppen fanden sich degene-

Table 1

Numbers and age of animals used for different substances and intervals between injection and termination

Substance	Survival time	8-day-old rat	11-day old rat
$^{99}Tc^m$-pertechnetate	30 min	2	
	3 h	2	
$^{99}Tc^m$-labelled pyrophosphate	30 min	2	1
	3 h	1	2
^{32}P labelled pyrophosphate	30 min	1	
	3 h	1	
^{85}Sr-chloride	30 min	2	
	3 h	1	

the dental hard tissues Therefore, it was considered of interest to perform autoradiography to determine the distribution of the substance with special reference to the dental tissues In contrast to techniques, based on preselection of certain tissues, whole-body autoradiography gives a general view of the distribution in practically all tissues of the body and therefore favours the making of unexpected findings, e g an unforeseen specific localization The distribution of $^{99}Tc^m$-labelled pyrophosphate was also compared with that observed for two other bone-seeking compounds, namely ^{32}P-labelled pyrophosphate and ^{85}Sr-chloride An estimation of the distribution of free pertechnetate was also included

Material and Methods

Labelled compounds Carrier-free $^{99}Tc^m$-pertechnetate was obtained as a NaCl eluate from a $^{99}Mo/^{99}Tc^m$ generator (Philips-Duphar) Each animal was given a dose of 2 5 to 3 0 mCi

$^{99}Tc^m$-labelled pyrophosphate was prepared by adding 5 ml $^{99}Tc^m$-pertechnetate eluate to a commercially available kit (TechneScan PYP, Mallinckrodt) Each vial contains 4 0 mg $SnCl_2$ $2H_2O$ and 20 0 mg $Na_4P_2O_7$ $10H_2O$ Each animal was given a dose of 1 8 to 2 6 mCi in 1 8 to 2 0 mg of sodium pyrophosphate

For comparison ^{85}Sr as chloride (AB Atomenergi, Studsvik) was used and each animal was given a dose of 0 06 mCi in 0 01 mg strontium chloride From the ^{32}P-labelled pyrophosphate (New England Nuclear Corporation) a dose of approximately 0 03 mCi containing 8 6 mg of pyrophosphate was given to each animal

Animals Twelve 8-day-old rats weighing about 19 g, and three 11-day-old rats weighing about 25 g, of the Sprague-Dawley strain, were used The number of animals used for each substance, and the intervals between injection and termination appear in Table 1

Table 2

Distribution of the different isotopes 30 minutes and 3 hours after injection in young rats

Substance	Bone	Dentine	Enamel	Stomach
$^{99}Tc^{m}$ pertechnetate	0	0	– – + +	+ +
$^{99}Tc^{m}$ labelled pyrophosphate	+ +	+ +	+	0
^{32}P labelled pyrophosphate	+ +	+ +	–	0
^{85}Sr-chloride	+ +	+ +	+	0

0 no uptake
low concentration
high concentration
+ – marked reduction of isotope from 30 min to 3 hours

Methods From the prepared solutions 0 1 to 0 5 ml were injected intraperitoneally into each animal The survival times were 30 minutes and 3 hours, respectively At the selected time, the animals were anaesthetized with ether and mounted on a microtome stage in carboxymethyl cellulose mixed with water The stage was immersed in a mixture of hexane and solid CO_2 (–75°C)

In a freeze-box (–15 C), sagittal sections through the whole animals were cut at different levels To obtain whole sections, an adhesive tape (No 688, 3 M, Minnesota Mining and Manufacturing Corporation) was applied to the section surface of the frozen specimen before cutting The sections, 20 μm thick, then adhered to the tape

Autoradiography was performed by apposition of the sections against Structurix D7 films (Agfa-Gevaert) Because of the short physical half-life of $^{99}Tc^{m}$, time did not allow the sections from animals injected with this isotope to dry in the cold before apposition against the films Therefore, the sections were kept frozen and pressed against the film in a freeze-room The ^{85}Sr- and ^{32}P-labelled sections were freeze-dried at –15 C for 2 days before apposition against the films During exposure the films and sections were stored in a freeze-box at –15°C $^{99}Tc^{m}$- and ^{32}P labelled sections were exposed for 2 days and ^{85}Sr-labelled sections for 4 days After exposure the sections were separated from the films and the $^{99}Tc^{m}$-labelled sections were allowed to freeze dry at –15°C

The films were developed in Gevaert G 138 for 2 1/2 min (+20°C) and fixed for 30 min in Gevaert G 334 Finally, the sections were stained with hematoxylin and eosin and mounted on glass slides in Euparal The freeze sectioning and autoradiographic technique have been described in detail by ULLBERG (1954) and ULLBERG et coll (1971)

Results

The results with respect to various tissues and organs are summarised in Table 2

The distribution of the active isotopes after an intraperitoneal injection of $^{99}Tc^{m}$-labelled pyrophosphate, ^{32}P labelled pyrophosphate and ^{85}Sr-chloride was similar

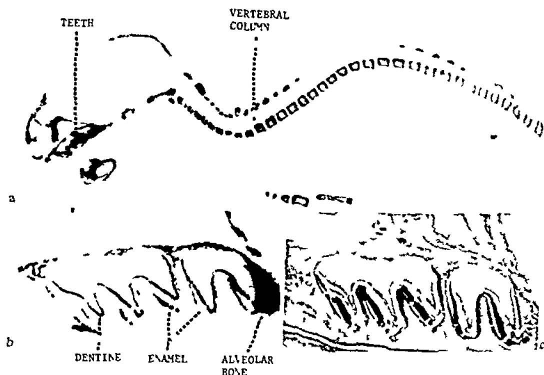


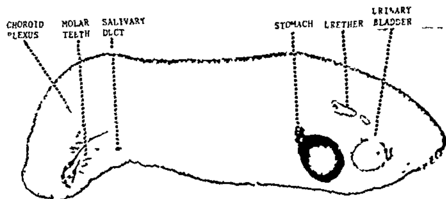
Fig 4 a) Autoradiogram from an 8-day-old rat 30 min after an i p injection of ^{85}Sr-chloride High concentration in bone and teeth b) Detail of an autoradiogram of the upper jaw from the same animal c) the corresponding section Uptake in the enamel is mainly confined to the cervical region and to the tip of the cusp A narrow zone of activity close to the dental pulp in the dentine

of the isotope could be observed in bone A marked accumulation was found in the stomach, intestines, sebaceous glands fur and developing enamel High concentration also occurred in the choroid plexus of the brain The uptake in the salivary glands was insignificant but intense uptake was found in the salivary ducts In the kidney *the concentration was moderate The contents of the urinary bladder were lost but* a high concentration was found on the walls of the urinary bladder and the ureters

Three hours after injection the distribution of the isotope was rather similar to that observed 30 min after injection No activity was observed in bone and dentine However, the enamel had lost most of its activity A high concentration of the isotope was found in the stomach, intestines sebaceous glands and in the fur Moderate concentration was visible in the urinary system

Discussion

Whole body autoradiography proved to be a suitable method to obtain information on the distribution of ^{99}Tc^{m} labelled pyrophosphate in spite of its short physical half life In the case of the two ^{99}Tc^{m} compounds the thickness of the sections the time of the exposure and development of the films were held constant The doses of



a



b



c

$^{99}Tc^m$ were about the same Thus, the method, to some extent, allows semi quantitative estimations of the exposure of the film and comparison of the concentrations of the isotope in the tissues at different time intervals after injection

From a clinical standpoint, the most interesting results with respect to the mineralizing tissues were the rapid and selective uptake of the isotope in bone and dentine after injection of $^{99}Tc^m$ labelled pyrophosphate, and the absence of uptake in bone and dentine of $^{99}Tc^m$ pertechnetate Concentrations of $^{99}Tc^m$ labelled pyrophosphate in the soft tissues were low These findings are in agreement with the results reported by HOPKINS et coll (1973) and HOSAIN (1973), who determined the activity of collected samples of different organs, and by DOPPELFELD & KUTZIM (1973) who used autoradiography Also, the initial rapid urinary excretion indicated by the autoradiograms was in accordance with these reports The accumulation of the isotope in the urinary tract after injection of $^{99}Tc^m$ labelled pyrophosphate may interfere with the image of bone anatomy and pathology in these regions, when the substance is used for clinical examinations

The distribution of $^{99}Tc^m$ labelled pyrophosphate in bone was similar to that of ^{32}P labelled pyrophosphate and ^{85}Sr The accumulation occurred mainly in the

amines play an important neurotransmitter role in the central nervous system, the investigation of the excretion of their metabolites in the patients with irradiated brain tumours seemed to be interesting Data about the radiation sensitivity of the brain tissue are rather controversial Light microscopy has indicated that very high doses of ionizing radiation are required to impair the structure of the nervous system Therefore, the nervous tissue was considered to be very resistant to radiation Later it was found that the brain functions and behaviour may be altered with very small doses of radiation, and the previous conception was submitted to criticism (LEBEDINSKY et coll. 1958, GANGLOFF & HALEY 1960, HUNT & KIMELDORF 1964) Blood vessels and glial cells were found to be more susceptible to the radiation injury than neurons, and white matter more than gray (RUBIN & CASARETT 1968) If the neurons are directly injured by irradiation or if the nerve cell injury is secondary to the impairment of blood vessels or glial cells, is not definitively known as yet Anyway, the described abnormalities provoked by irradiation have in its biochemical basis the release of neurotransmitter substances such as biogenic amines

Material and Methods

Thirteen patients of different sex and age and with brain tumours of various location and type were irradiated (Table 1) Before irradiation the tumour tissue was removed as radically as possible in all cases Fifteen to 30 days postoperatively, the operated region was submitted to telecobalt therapy (Gammatron 3, Siemens) The irradiated field was always 3 cm wider than the border of the removed tumour tissue The remaining part of the head was shielded The dose was dependent upon the clinical condition of the patient, those in relatively good general condition, and without signs of disturbed brain function, were given higher daily doses from the beginning, those with symptoms or signs of some brain disturbance (related to increased intracranial pressure or similar) were irradiated with more caution because of the possibility of inducing brain oedema Thus, each patient had his own schedule of irradiation The dose-rate was 100 R/min, and focus to skin distance 75 cm

24-hour urine of these patients was collected under toluene in the control period (3 days before irradiation) as well as during the first 3 days of irradiation This whole time the patients were on a diet avoiding food and drinks which might have some influence on the metabolism of the determined compounds

The following metabolites of biogenic amines were determined in urine 5-hydroxyindoleacetic acid (5 HIAA)—the main metabolite of 5-hydroxytryptamine (DALGLIESH 1958), the metabolites of catecholamines i e vanillinmandelic acid (VMA) and free 3 methoxy-4-hydroxy-phenylglycol (MHPG) both by the method of SAPIRA (1968) In all urine samples creatinine was also determined as the referent substance (FOLIN 1954)

The results are evaluated statistically by the t-test using 'method of differences' which is specially convenient for small sample of dependent variates (FISCHER 1950)

Table 1

The material of patients with irradiated brain tumours

Case No	Age and sex	Brain tumour (Type and location)	Irradiation Area	Field size (cm)	Dose (R)
1	63 M	Gliosarcoma (temp occipit)	Temporooccipital	10 × 9	200, 200, 200
2	31 M	Oligodendroglioma *malignum (front pariet)*	Frontoparietal	8 × 10	100, 100, 100
3	9 F	Medulloblastoma (vermis)	Posterior cranial fossa	11 × 7	300, 300, 300
4	54 F	Glioblastoma (front temp)	Frontotemporal	8 × 10	100, 200, 300
5	26 M	Reticulosarcoma (front)	Frontotemporal	9 × 9	100, 100, 150
6	29 M	Transitional oligodendroglioma	Parietotemporo-occipital	10 × 13	50, 100, 100
7	30 M	Recurrent transitional oligodendroglioma (pariet temp)	Parietotemporal	11 × 11	50, 100, 100
8	48 M	Malignant tumour (meningiosarcoma?)	Frontotemporal	8 × 11	200, 200, 200
9	16 F	Cerebellar sarcoma	Posterior cranial fossa	8 × 10	300, 300, 300
10	67 F	Pituitary adenoma	Temporal	5 × 5	200, 200, 200
11	34 F	Gliosarcoma (pariet temp occipit)	Parietotemporo-occipital	10 × 14	400, 400, 500
12	60 F	Glioblastoma (pariet. temp occipit)	Parietotemporo-occipital	16 × 12	500 500, 500
13	43 F	Mixed transitional glioma (pariet occipit)	Parietotemporo-occipital	10 × 13	400, 400, 400

Results

The excretion of the determined metabolites of biogenic amines in the patients with irradiated brain tumours appears in Table 2 The control values represent the mean 24-hour excretion of the related metabolites in all patients during the 3 pre-irradiation days The quantities of the excreted metabolites in the course of radiation therapy are presented for all patients together as the mean excretion for each of the 3 first days separately The highest 5-HIAA excretion as well as that of MHPG occurred on the second day of irradiation, but the VMA excretion increased gradually until the third day In some of these patients the excretion of the mentioned metabolites was followed for longer than 3 days, but these values are again in the range of the control ones Fig 1 demonstrates the excretion of 5-HIAA in each of 12 patients with irradiated brain tumours If two groups of 5-HIAA values (control and irradiated) are compared, a significant 5-HIAA increase ($p < 0.02$) during irradiation is found When the 5-HIAA excretion of each day of irradiation is compared separately

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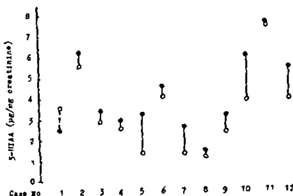


Fig 1 5-HIAA excretion Mean values of 3 days obtained in the course of irradiation (●) are compared to mean values of 3 days in the control period (○) ○—● positive difference ●-○ negative difference (p<0 02)

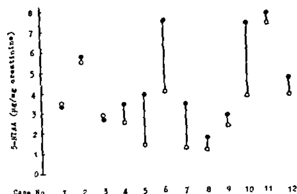


Fig 2 5 HIAA excretion The second day of irradiation (●) is compared to mean values of 3 days in the control period (○) ○—● positive difference (p<0 01)

MHPG in the second day of irradiation might be explained in a similar way It is known that the quantity of catecholamines is decreased in the organs of irradiated animals (McGoodall & Long, Varagić et coll, van Woert & Korb 1970) and increased in the urine (Braun & Kuschke, Franzen et coll, McGoodall) As a reflection of the local release of catecholamines in patients with irradiated abdomen (Ra therapy) a significantly enhanced excretion of all catecholamine metabolites, except MHPG has been found (Peričić) This might indicate a different origin of MHPG from that of other catecholamine metabolites The hypothesis about the most central origin of MHPG was supported by many authors (Mannarino et coll 1963, Maas & Landis 1966 1968, Schanberg et coll 1968, Scharman 1969, Maas et coll 1972) Significant increase of this metabolite in the patients with irradiated brain tumours would also lend support to this hypothesis Certainly the mentioned increase could be more expressed in the case that the estimation of the total (i e free plus conjugated) urinary MHPG has been possible

Table 2

The metabolites of biogenic amines in urine (Mean values ± S E)

	5-HIAA µg/mg creatinine (N = 12)	VMA µg/mg creatinine (N = 13)	MHPG µg/mg creatinine (N = 13)
Control*	3 321 ± 0 314	3 478 ± 0 244	0 863 ± 0 055
Radiation therapy			
First day	3 906 ± 0 682	4 054 ± 0 419	0 940 ± 0 136
Second day	4 623 ± 0 606	4 618 ± 0 762	1 287 ± 0 180
Third day	3 864 ± 0 681	5 018 ± 0 883	1 135 ± 0 213

* Mean value of 3 pre irradiation days ± S E

with control values, a more significant 5-HIAA increase ($p < 0\ 01$) appears on the second day of treatment (Fig 2)

The comparison of MHPG excretion in the pre-irradiation period and MHPG excretion on the second day of irradiation (Fig 3) also shows a significant difference ($p < 0\ 05$) However, the mean excretion value of this metabolite during three days of irradiation does not show any significant difference compared to the control value

The excretion of another catecholamine metabolite—VMA—in the same patients is presented in Fig 4 The mean VMA values obtained during the 3 days give a significant difference ($p < 0\ 05$) in comparison to the control values The highest mean VMA excretion (Table 2) is expressed on the third day, but because of the great variations this difference is regarded as non-significant

Discussion

It is well known that whole-body irradiation of animals is followed by a decrease of 5-hydroxytryptamine in brain tissue (ERSCHOFF et coll 1962, PALAIĆ & SUPEK, PAUSESCU et coll 1973) A diminished 5-hydroxytryptamine concentration after the irradiation occurs also in other organs e g spleen and small intestine, and this leads to an increase of this metabolite in urine Enhanced 5-HIAA excretion has been observed in most patients locally irradiated (SMITH & LANGLANDS, PERIČIĆ & DEANOVIĆ) In the present patients, the increased amount of 5-HIAA in urine is presumably due to a local release of 5-hydroxytryptamine from the irradiated brain tissue The excretion of 5-HIAA is increased specially on the second day of radiotherapy ($p < 0\ 01$) This finding is in accordance with the data of other authors (WILLOUGHBY, PALAIĆ & SUPEK), who have shown the maximum drop of 5-hydroxytryptamine 48 hours after irradiation in the intestine as well as in the brain Moreover, in the present patients an additive effect of 2 initial radiation doses might occur

It seems that the significantly increased excretion of noradrenaline metabolite

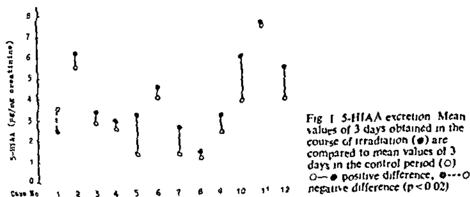


Fig 1 5-HIAA excretion Mean values of 3 days obtained in the course of irradiation (●) are compared to mean values of 3 days in the control period (○) ○—● positive difference, ●---○ negative difference ($p < 0\ 02$)

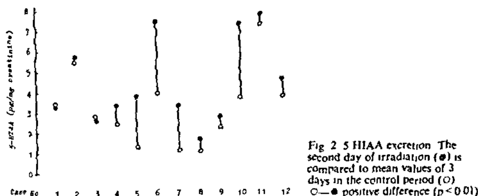


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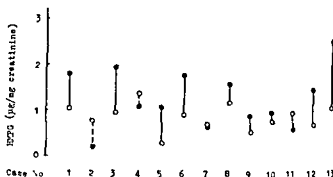


Fig 3 MHPG in urine The second day of irradiation (●) is compared to mean values of 3 days in the control period (○) ○—● positive difference, ●---○ negative difference ($p < 0.05$)

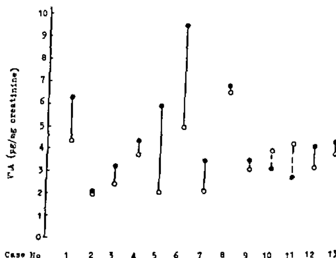


Fig 4 VMA in urine Mean values of 3 days obtained in the course of radiotherapy (●) are compared to mean values of three days in the control period (○) ○—● positive difference, ● --○ negative difference ($p < 0.05$)

However, the excretion of VMA during the course of irradiation is different The excretion of this catecholamine metabolite is significantly increased during the whole period (3 days of irradiation), whereas the VMA excretion in none of the single days has been markedly aberrant from the control, but it climbs gradually till the third day of irradiation The reason for the delayed and progressively intensified VMA excretion may be due to the secondary inclusion of the peripheral sympathetic system in the response of the organism to the irradiation of brain tumours It has been shown that the sympathetic adrenergic nerves contribute only to a very small extent to the total number of brain noradrenaline nerve terminals (SACHS & JONSSON 1973) A greater part of adrenergic nerves in the brain represent the ascending axons belonging to the dorsal noradrenaline bundle (UNGERSTEDT 1971) It is possible that the estimated MHPG reflects the released noradrenaline from both groups of adrenergic terminals in the brain On the other hand, the enhancement of the VMA excretion, mainly the metabolite of the peripheral released noradrenaline (MAAS et coll), may not occur before the activation of the peripheral sympathetic adrenergic system takes place For a general reaction of the whole sympathetic adrenergic system (central and

peripheral) pleads also the uniform reaction of this system in response to stimulation by drugs (VOGT 1954), as well as in response to stress induced by different physical stimuli (MAYNERT & LEVI 1964) The stimulation of the peripheral sympathetic neurons during the course of irradiation of brain tumours may occur in a neural way, it is known that an intimate synaptic contact between the endings of noradrenaline containing neurons and the sympathetic preganglionic neurons exists in the intermediolateral columns of the spinal cord (DAHLSTRÖM & FUXE 1965)

Although the clinical material was fairly heterogenous, some comparisons between the similar cases and their biochemical reactions are possible However, any explicit dependency of the monoamine metabolites excretion on the type and location of tumour was not observed No correlation existed neither in comparison with the irradiated surface and the dose, nor in comparison with the radicalness of the operation In some patients a marked clinical improvement during the first days of irradiation was accompanied by an excessive increase in the excretion of all metabolites examined (for instance in case 5), but this relationship was not clear in other cases Attempts to correlate the biochemical response with the appearance or absence of early signs of radiation sickness (nausea, vomiting, etc) did not give positive results The excretion of metabolites of biogenic amines in the patients with irradiated brain tumours was neither dependent on the time interval between the operation and the beginning of radiation therapy The sham irradiation, which has been done in some cases did not change the excretion of metabolites of biogenic amines, thus the above described phenomena are certainly not a nonspecific stress reaction but a process directly induced by irradiation and submitted to individual variations

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SUMMARY

The metabolites of biogenic amines were determined in the 24-hour urine samples of

[illegible] radiation induced release of their parent amines from the brain in the case of VMA the secondary response of the peripheral sympathetic system might occur

ZUSAMMENFASSUNG

Es wurden die Metaboliten biogener Amine in 24-Stunden Urin Proben von Patienten, *die nach chirurgischer Entfernung eines malignen* Gehirntumors nachfolgend einer Tele cobolt Therapie der entsprechenden Kopf Region ausgesetzt worden waren, untersucht Es wurde ein signifikanter Anstieg der Ausscheidung von *5-Hydroxyindolessigsaure* (5 HIAA), Vanillinmandelsäure (VMA) sowie von freiem 3-Methoxy-4-Hydroxy Phenolglykol (MHGG) wahrend der Bestrahlungs Periode gefunden Dieser Anstieg ist hauptsachlich das Ergebnis einer Strahlen bedingten Freisetzung der ursprunglichen Amine vom Gehirn im Fall von VMA mag eine sekundare Antwort des peripheren sympathischen Systems vorliegen

RÉSUMÉ

Les auteurs ont dosé les métabolites des amines biogéniques sur des prélèvements d urine de 24 heures de malades soumis à une exérèse chirurgicale d'une tumeur cérébrale maligne puis traités par télécobalthérapie de la region correspondante de la tete Ils ont constaté une augmentation importante de l'excrétion de l'acide 5-hydroxyindoleacétique (*5 HIAA*) de l'acide vanillinemandélique (VMA) ainsi que du 3 méthoxy-4-hydroxy-phénylglycol libre (MHPG) au cours de la période d'irradiation Cette augmentation est vraisemblablement le résultat d'une liberation, sous l'effet des radiations, à partir du cerveau de leurs amines *parentes, dans le cas du VMA, pourrait intervenir la reponse secondaire du systeme sympathi* que périphérique

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FROM THE POSTGRADUATE MEDICAL INSTITUTE, PEDIATRIC DEPARTMENT, AND GENETIC LABORATORY, INSTITUTE OF HYGIENE AND EPIDEMIOLOGY, PRAGUE, CZECHOSLOVAKIA

INFLUENCE OF DIAGNOSTIC ROENTGEN DOSES ON HUMAN CHROMOSOMES AND INFLUENCE OF AGE ON THE ABERRATION YIELD

MARIA KUCEROVÁ, ZDENKA POLÍVKOVÁ and LIBUSE HRADCOVÁ

It has been known for fifteen years that in vivo irradiation with high roentgen doses induces structural changes in human chromosomes of peripheral lymphocytes and other tissues It is also known that aberrations are mostly of the chromosomal type, i e most of them are dicentrics, fragments and ring chromosomes The number of chromosomal aberrations in peripheral blood cells increases proportionally after high doses

Nevertheless, the influence of low doses on human cells is far from being completely clear The literature available contains little information (BLOOM & TJIO 1964, REISMAN et coll 1967) The data in these reports were obtained from a non-homogenous sample of patients irradiated in different ways, and the number of cells scored was not high Insignificantly increased numbers of aberrant cells were found in both materials UNSCEAR (1969) believes that only an automatic analysis of human chromosomes may give a correct answer to this problem

In previous experiments (KUCEROVA et coll 1972) the effect of low doses of roentgen irradiation in vitro on chromosomes of human cells was analysed A significant increase of chromosomal aberrations was found only after doses ranging between

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Table 2

Influence of radiation doses at urography on chromosomes of a group of 6 children 8–32 month old

Blood samples	Type of aberration	No of aberrations	Per cent of cells with aberration	Total No of cells analysed
Control	Fragment	6	0 4	1 500
Immediately after irradiation	Fragment	13		
	Dicentric	2		
	Σ	15	0 8	1 800
24 hours after irradiation	Fragment	13		
	Dicentric	7		
	Σ	20	1 1	1 800

Results and Discussion

No significant differences were found between the results of the 10 subjects in the first group and between the 6 subjects in the second group which permitted the pooling of the results The pooled data appear in Tables 1 and 2

The total number of cells scored in each type of sample varied from 1 500 to 2 500 A distinctly increased number of aberrant cells was found following irradiation, but this increase was significant only in samples collected 24 hours after irradiation (at level $p<0\ 01$) *and only in the first group of patients (skin dose about 3 5 R) In* the group of young children, the increase of aberrations was higher in samples collected 24 hours after irradiation, but the significant level was only $p<0\ 05$ (skin dose about 1 R)

If the number of aberrant cells in both groups of patients are compared, it is found that the level of aberrations in young children was lower in all types of samples including control ones It may be supposed that these children had had only short periods of time to be exposed to all sources of irradiation as well as to other mutagenic factors Direct measurement of skin doses demonstrated that the younger the children, the lower were the doses used for urography, because of less body thickness This explains the lower number of aberrations recorded after irradiation in the second group

The number of dicentric and ring chromosomes is supposed to be a most reliable indicator of human radiation sensitivity if routine cytogenetic methods are used (UNSCEAR) Therefore the number of dicentrics and rings per cell in all samples of both groups of patients irradiated in vivo were compared with previous results obtained after in vitro irradiation of human lymphocytes (KUČEROVÁ et coll) The

... of the number of aberrations in all control samples were very

Table 1

Influence of radiation doses at urography on chromosomes of a group of 10 persons 7-18 years old

Blood samples	Type of aberration	No of aberrations	Per cent of cells with aberration	Total No of cells analysed
Control	Fragment	12		
	Dicentric	2		
	Σ	14	0 8	1 687
Immediately after irradiation	Fragment	26		
	Dicentric	6		
	Ring	1		
	Σ	33	1 32	2 506
24 hours after irradiation	Fragment	25		
	Dicentric	7		
	Ring	1		
	Σ	33	2 0*	1 627

* Significantly higher comparing with control data

15 and 30 R or higher The scoring of 1 500 cells per dose allowed a determination of this sensitivity level of human cells

In an attempt to elucidate the influence of low doses in vivo, it was decided to analyse in detail peripheral blood chromosomes in 16 young subjects, irradiated with diagnostic doses during urography

Material and Methods

The same machine (Chirodur 125, with Rotax lamp 125) was used for the exposures (filter 1 mm Al, 50-55 kV, 70-150 mAs, FFD 90 cm) The only variable factors were the age, size and weight of the patients The total skin dose was measured with a Victoreen apparatus and was found to vary between 1 and 4 R, in a 3 years old patient it was 1 002 mR (the thickness of the body 11 cm) and in a 17 years old patient 3 445 mR (the thickness of the body 15 cm)

Two groups of patients of different ages were chosen The first group comprised 10 persons aged 7 to 18 years, the second group consisted of 6 children at the age of 8 to 32 months The urography was indicated because of possible infection of the kidneys None of the patients was given cytostatics or other drugs with known mutagenic activity

Blood samples were taken before irradiation, immediately after and 24 hours after the irradiation Lymphocytes were cultivated for 58 hours using a routine cytogenic microtechnique (HUNGERFORD 1965) Slides were stained by Giemsa Chromosomal aberrations were scored as recommended by UNSCEAR and WHO (BUCKTON & EVANS 1973) All slides were coded and scored blindly

methods if a sufficiently high number of cells is analysed In the age group between 8 months and 18 years there is no evident influence of age on the radiation sensitivity of human lymphocytes in vivo

Acknowledgement

We are grateful to Dr Vladimír Matoušek, from the Institute of Experimental Biology and Genetics of the Czechoslovak Academy of Sciences for his assistance in the mathematical evaluation of our results

SUMMARY

Urography was performed in 2 groups of patients (one comprising patients aged 7–18 [illegible]

blood samples taken 24 hours after irradiation No age-dependent influence on the radiation sensitivity in vivo was found

ZUSAMMENFASSUNG

Es wurde eine Urographie bei zwei Gruppen von Patienten (die eine umfasste Patienten im Alter von 7 bis 18 Jahren die andere Patienten im Alter von 8 bis 32 Monate) unter konstanten Bedingungen durchgefuhrt Die Hautdosis lag zwischen 1 und 4 R Es wurden Blutproben vor unmittelbar nach und 24 Stunden nach der Bestrahlung entnommen Es wurde ein signifikanter Anstieg von aberranten Zellen nur in den Blut Proben die 24 24 Stunden nach der Bestrahlung entnommen wurden gefunden Es wurde kein altersabhangiger Einfluss der Strahlenempfindlichkeit in vivo gefunden

RESUME

Une urographie a été faite à deux groupes de malades (l un comprenant des malades ages de 7 à 18 ans l autre des malades ages de 8 a 32 mois) dans des conditions constantes La dose à la peau a varié entre 1 et 4 R Des prelèvements sanguins ont été faits avant immediatement après et 24 heures après l irradiation C est seulement dans les prelèvements sanguins pris 24 heures après l irradiation qu on a trouvé une augmentation significative du nombre des cellules aberrantes Les auteurs n ont pas trouvé de variations de la radio sensibilité in vivo en fonction de l age

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Table 3

Comparison of number of dicentrics and rings per cell after irradiation in vitro and in vivo

Blood samples	No of dicentrics and rings	Total No of cells analysed	No of dicentrics and rings/cell
In vitro			
Control	2	1 500	0 0013
Dose 5 R	2	1 500	0 0013
10 R	2	1 500	0 0013
15 R	5	1 500	0 0033
30 R	26	1 500	0 0173
In vivo			
Persons 7–18 years old*			
Control	2	1 687	0 0012
Immediately after irradiation	7	2 506	0 0028
24 hours after irradiation	8	1 627	0 0049
Children 8–32 month old**			
Control	0	1 500	0 0000
Immediately after irradiation	2	1 800	0 0011
24 hours after irradiation	7	1 800	0 0038

* Skin-dose 2–4 R

** Skin dose max 1 R

similar The number of aberrations found after skin doses ranging between 1 and 4 R may be compared with the number obtained in lymphocytes irradiated in vitro with 15 R The number of aberrations after the low skin doses were higher than expected

An increased number of chromosomal aberrations during the first 24 hours after in vivo irradiation was first reported by BUCKTON et coll (1971), who analysed the effects of whole body irradiation with high doses The present results are in full concordance with those of these authors They assumed that the cells with chromosomal aberrations are liberated from lymphopoietic centers during the first 24 hours Another possibility may be that the breaking and rejoining process continues during the first hours after irradiation and elevates the number of chromosomal aberrations

LINIECKI et coll (1971), SASAKI (1971) and SASAKI et coll (1970) have supposed that age has an influence on the radiation sensitivity of human chromosomes SASAKI mentioned a higher increase of chromosomal aberrations after irradiation of lymphocytes of young children, i e in the first three years of age The results presented by these authors were obtained after experimental in vitro irradiation In the present material no age dependence in the numbers of chromosomal aberrations after in vivo irradiation was found This may indicate that there is a difference between the sensitivity of cells in vitro and in vivo

Finally it may be concluded that common diagnostic irradiation induces chromosomal aberrations in peripheral lymphocytes detectable by routine cytogenetic

A C T A R A D I O L O G I C A

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TISSUE HETEROGENEITY IN THE ANTERIOR CHEST WALL AND ITS INFLUENCE ON RADIATION THERAPY OF THE INTERNAL MAMMARY LYMPH NODES

B LINDSKOUG and A HULTBORN

Investigation of tissue heterogeneities

This report is a continuation and revision of a previous work concerning distribution of the absorbed dose in post-operative irradiation of regional lymph nodes in mammary carcinoma (RAGNHULT et coll 1972) On the basis of experimental measurements it was demonstrated that a considerable distortion of the absorbed dose distribution occurred when lymph glands along the internal thoracic vessels were irradiated with high energy electrons The absorption of electrons will depend on the stopping power, which is approximately proportional to the electron density of the absorbing medium, i e the most important of the parameters influencing the interaction of electrons with matter In the previous report it was realised that a survey of the electron densities of the various tissue materials in the anterior chest wall was needed A method for determination of electron density of fresh autopsy specimens without loosing clinical aspects was developed and tested with materials of well known composition Further measurements have now been per-

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Table 2

Results of density measurements Number of specimens measured within brackets (SD = standard deviation)

Cartilage, bone

Specimen number	Costal cartilage		Rib bone		Sternum	
	g cm⁻³	SD	g cm⁻³	SD	g cm⁻³	SD
1	(5) 1 137	0 013	(3) 1 298	0 042	(1) 1 266	
2	(6) 1 138	0 006	(6) 1 277	0 018	(1) 1 123	
3	(6) 1 126	0 005	(6) 1.208	0 023	(1) 1 096	
4	(6) 1 116	0 009	(5) 1 142	0 028	(2) 1 065	0 012
5	(6) 1 126	0 008	(6) 1 203	0 024	(2) 1 093	0 004
6	(6) 1 119	0 003	(6) 1 170	0 026	(4) 1 050	0 003
Over all mean value	(35) 1 127	0 011	(32) 1 211	0 057	(11) 1 091	0 063

Soft tissues

Specimen number	Muscle tissue		Muscle tissue with fat		Fatty tissue	
	g cm⁻³	SD	g cm⁻³	SD	g cm⁻³	SD
7	(2) 1 056	0 003			(2) 0 940	0 005
8			(3) 1 034	0 006	(5) 0 918	0 003
Over all mean value	(2) 1 056	0 003	(3) 1 034	0 006	(7) 0 924	0 011

Remark

Specimen No 7 Tissue from m pectoralis Visible courses of connective and fatty tissue were removed
Fatty tissue from subcutis anterolaterally on the thorax and from the abdominal wall

Specimen No 8 Tissue from m pectoralis and m serratus anterior with many courses of connective and fatty tissue
Subcutaneous fatty tissue from the mammary region

possible Soft tissue was removed from the surfaces of sternum, ribs and costal cartilage by dissection (Fig 2)

Determination of density The density was determined by weighing the spe-

[illegible] at room temperature, which varied between 20 and 24 C The specimens were suspended in the balance by a thread Material with a density less than 1 was provided with a sinker The results of density determination are included in Table 2



Fig 1



Fig 2

Fig 1 Specimen No 2 of the anterior chest wall

Fig 2 Specimen No 4 of sternum, rib bone and costal cartilage

formed and complemented by a more comprehensive review of the pertinent literature Determinations were made on specimens from 8 autopsies

Preparation Ages and sexes of the patients appear in Table 1, together with the time-lag between death and autopsy Within a few hours post-mortem the bodies were transferred to cold storage and maintained at 4°C until specimens were removed, which in all cases occurred within four days

Fig 1 demonstrates a specimen of cartilage, bone and soft tissue from the anterior wall of the thorax—corresponding to a parasternal electron field In order to obtain results which could be considered valid and applicable in radiation therapy it was essential to avoid influencing the material mechanically and chemically, as far as

Table 1

Particularities of the specimens used

Specimen number	Age	Sex	Delay between death and autopsy (days)
1	63	M	0 5
2	49	F	4
3	54	F	1
4	61	F	1
5	76	F	3
6	66	M	3
7	81	F	3
8	61	F	1

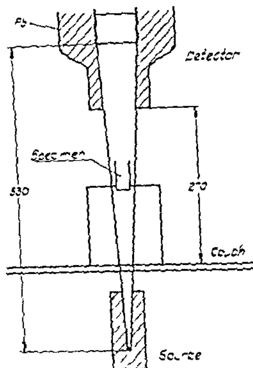


Fig 3 Principle for transmission measurements The radiation source ^{137}Cs The specimen is placed in a beaker Dimensions in mm

If a specimen in the beaker can be assigned an effective cross-sectional area, A_{eff}, for which the exponential relationship (1) is approximately valid and introducing the parameter,

$$F = \frac{_e\sigma}{A_{eff}} \tag{3}$$

is obtained

$$I = I_0 \exp\left[-Fm\eta\right] \tag{4}$$

F will be dependent upon geometry and mass of the specimen and if different volumes were used considerable errors might occur

Before and after each preparation measurement the reference material (distilled water) was introduced in the radiation beam and the counting rate recorded The following notations were introduced

I_r and I_{or}, number of counts per minute with reference material and empty beaker respectively,

m_p and m_r, mass of specimen and reference material, respectively, in grams,

η_p and η_r, number of electrons per gram for specimen and reference material, respectively

Extraction of fatty tissue and creation of air cavities in the spongy parts of sternum and ribs had to be avoided as far as possible (cf DEBOIS et coll 1969) Especially close to the cut surfaces in sternum and ribs, the spaces between the trabeculae have a tendency to trap air bubbles or fluid In order to estimate the error under those conditions two series of measurements were performed on specimen 3 The maximum deviation occurred, as expected, for ribs, and amounted to 0 012 g cm^{-3}

Immediately after the density determination the specimens were closely packed into plastic beakers for the determination of electron content

Determination of electron content Since it was a prerequisite that the results should be clinically applicable, narrow-beam geometry, which requires fresh autopsy specimens in the form of plane discs, could not be used An apparatus designed for determination of the mineral content of lumbar vertebrae by measurement of transmission (ROOS et coll 1970) proved to be well suited for the purpose The radiation source consisted of ^{137}Cs which decays under emission of photons with an energy of 662 keV At this photon energy the interaction with matter is strongly dominated by the Compton effect As the average Compton collision cross-section per electron depends only on the photon energy, the probability of an interaction between a photon and the specimen will depend only on the electron content of the material Thus, by determining the attenuation of the photon beam for a specimen of unknown composition and comparing the result with the attenuation obtained for a well known reference material, the electron content of the specimen could be determined

The design of the measuring equipment is illustrated in Fig 3 During measurements the preparations were stored in plastic beakers (diameter 25 mm, height 50 mm)

Theoretical considerations The following notations were used

I, number of counts per minute

$\left(\frac{\mu}{\varrho}\right)$, mass-attenuation coefficient (cm^2 g^{-1})

${}_e\sigma$, Compton attenuation cross-section per electron (cm^2)

ϱx, dimension of the specimen (g cm^{-2})

m, mass of the specimen (g)

A_{eff}, effective area of the specimen in the plane of measurement (cm^2)

η, electron content (g^{-1})

The common exponential expression for the attenuation of a photon beam is only valid with narrow-beam geometry

$$I = I_0 \exp\left[-\left(\frac{\mu}{\varrho}\right)\varrho x\right] \tag{1}$$

The mass attenuation coefficient (μ/ϱ) may also be written as

$$\frac{\mu}{\varrho} = \eta\,{}_e\sigma \tag{2}$$

Table 4

Results of electron content determination of specimen

Cartilage, bone

Specimen number	Costal cartilage $g^{-1} \times 10^{-24}$	Rib bone $g^{-1} \times 10^{-24}$	Sternum $g^{-1} \times 10^{-24}$
5	0 321	0 309	0 324
6	0 309	0 294	0 317
Mean value	0.315	0 302	0 320

Soft tissues

Specimen number	Muscle tissue $g^{-1} \times 10^{-24}$	Muscle tissue with fat $g^{-1} \times 10^{-24}$	Fatty tissue $g^{-1} \times 10^{-24}$
7	0 334		0 334
8		0 330	0 330
Mean value	0 334	0 330	0 332

Specimens 7 and 8 see remark Table 2

The most important errors probably originate from variations in the scatter contribution for the different materials Thus, the shape of the specimen and the filling of the beaker will influence on the magnitude of the error This point was indicated by the test measurements In Table 3 results with different-shaped perspex were included Cylindrical rods of various dimensions gave a deviation of 1.2 per cent with loose packing but only 0 6 per cent with tight packing Small pieces of crushed perspex gave the same result as for a homogeneous rod, deviating only 0 3 per cent from the calculated value Powder with very high density (2 5 g cm^{-3}) and a liquid with very low density (0 89 g cm^{-3}) gave a deviation of +1 7 per cent and −1 8 per cent, respectively Obviously, a close filling with a homogeneous material of a density of the same magnitude as the reference material will give the best results

Examination of specimens Immediately after preparation and determination of density the specimens were submitted to transmission measurements

1) The balance was adjusted to zero with the empty beaker The beaker was then filled with the specimen as closely packed as possible The weight of the specimen was recorded
2) The counting rate was measured with an empty beaker in the beam
3) The empty beaker was filled with distilled water and the weight was determined
4) The counting rate was measured with the distilled water in the beam
5) The counting rate was measured with the specimen in the beam
6) The weight of the distilled water was recorded
7) The weight of the specimen was recorded
8) Measurement number 2 was repeated

Table 3

Results of electron content determination of test material Comparison with calculated values Calculated electron content included

Material	Electron content $g^{-1} \times 10^{-23}$		Density $g\ cm^{-3}$	Electron density $cm^{-3} \times 10^{-24}$
	Calculated	Measured		
Perspex $C_5H_8O_2$				
Homogeneous rod*	0 324	0 325	1 186	0 385
Loosely packed rods**		0 320		0 380
Tightly packed rods**		0 326		0 387
Crushed perspex		0 325		0 385
Tricalciumphosphate Powder (pro anal) $Ca_5(PO_4)_3(OH)$	0 300	0 305	2 528	0 771
Oleic acid Liquid $C_{17}H_{33}COOH$	0 337	0 331	0 887	0 294

* Dimension 25 mm × 20 mm

** Dimension 5 mm × 10 mm and 10 mm × 10 mm

If F had the same value for both specimen and reference material,

$$\frac{\eta_n m_n}{\eta_r m_r} = \frac{\ln(I_n/I_{on})}{\ln(I_r/I_{or})} \tag{5}$$

The masses of the specimen and the reference material were determined by weighing before and after the transmission measurements The electron content (η_r) for the reference material was calculated to be 3 34 10^{23} g^{-1} and the electron content of the specimen (η_n) was computed from the formula (6),

$$\eta_n = 3\ 34\ 10^{23} \frac{m_r}{m_n} \frac{\ln(I_n/I_{on})}{\ln(I_r/I_{or})} \tag{6}$$

Finally, the product of the densities of the specimens and the corresponding electron content gave the quantity sought, i e the electron densities for the specimens

Experimental tests of method To check the method a number of test materials of known compositions but different configurations were used Table 3 summarizes the results and also gives the calculated values, for comparison It was essential for several reasons to keep the counting rate approximately equal for both reference material and specimen (1) the statistical error should be of the same magnitude, (2) the ratio of the logarithms in equation (6) should be close to 1, thus, giving a minimum error of edge effects, (3) the scatter contribution to the counting rate should be of the same order of magnitude for both reference material and specimen

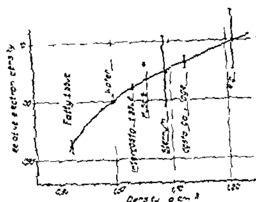


Fig 4

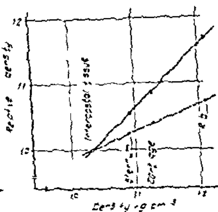


Fig 5

Fig 4 Relative electron density of tissues from the anterior chest wall

Fig 5 Relative density (——) and relative electron density (-) for sternum, costal cartilage and rib bone normalized to intercostal soft tissue

he found a considerable variation in density depending on the water content With 7 7 per cent H_2O he reports 0 924 and with 42 0 per cent H_2O 1 017 g cm^{-3} The water content was not considered in the present investigation

The results of the determinations of electron content appear in Table 4 *It is apparent that the variation in electron content in the anterior chest wall might amount* to about ±5 per cent

In Table 5 the over all mean values of density and electron content and the electron densities computed from the determined values in the different types of specimens are given and in the last column the ratios to the electron density for water

The relative electron densities for the various tissues in the anterior chest wall were plotted against density (Fig 4) As the water content of fatty tissues will influence the density, the value 1 017 g cm^{-3} found by TRUBESTEIN for fat containing 42 per cent H_2O must also be considered In that case the relative electron density will be 1 020 a value lying very close to the value found for intercostal tissue

Discussion

Several approximate methods have been proposed for calculating the influence of a heterogeneity on the distribution of absorbed dose in radiation therapy with electrons (DUTREIX 1966, POHLIT 1969, BOONE et coll 1969, DAHLER et coll 1969) However, no simple method seems to exist for those cases in which elastic scattering is the dominant effect This is the case for heterogeneities having small cross sectional areas and for regions where there is a great difference in electron density between the heterogeneity and the surrounding medium (KARJALAINEN et coll 1968) BRENNER et coll (1969) have demonstrated that scattering effects have a considerable

Table 5

Results of electron density determination in material from the anterior chest wall

Material	Density g cm^{-3}	Electron content g^{-1} × 10^{24}	Electron density cm^{-3} × 10^{24}	Relative electron density
Rib bone	1 211	0 302	0 366	1 099
Costal cartilage	1 127	0 315	0 355	1 066
Sternum	1 091	0 320	0 349	1 048
Muscle tissue*	1 056	0 334	0 353	1 060
Muscle tissue with fat	*1 034*	*0 330*	*0 341*	*1 024*
Fatty tissue	0 924	0 332	0 307	0 922
Water	0 997	0 334	0 333	1 000

* Connective and fatty tissue macroscopically removed

Measurement number 2 had to be repeated because of temperature drifting of the instruments Due to evaporation the specimens had to be weighed both before and after the transmission measurements The counting rate with empty beaker was of the order of 300 000 counts per minute For every measurement five values were registered, each integrated over one minute The mean value of the five readings were used for the calculations, which were performed using a desk calculator

The sternum caused special problems during preparation, since it is composed of highly vascular spongy bone with a marrow containing blood cells and fat cells enclosed in a thin compact bone The problems were overcome in the following way By means of a circular metal tube with a sharp edge a number of circular plates were punched out of the sternum in dorsoventral direction The tube was of the same internal diameter (25 mm) as the beaker in which he specimens were placed during measurement From the tube the plates were gently pushed directly into the beaker With this method liquids inside the sternum were preserved and the risk of changing the composition was exceedingly small

Results

The results of the density determinations in cartilage and bone are given in Table 2 As expected, the dispersion was greatest for spongy bones

In spite of the calcific deposits (Figs 1, 2) the costal cartilage varied only little in density The standard deviation is about 1 per cent The over all mean density of sternum was found to be 1 09 g cm^{-3} with a standard deviation of 0 06 Similar measurements on human sternum were made by BOONE et coll (1969), who reported a value of 1 15 g cm^{-3}

The soft tissue densities are in good agreement with the results reported by TRÜBESTEIN (1960) He reports for pectoralis major 1 050 g cm^{-3} at 36°C In fatty tissue

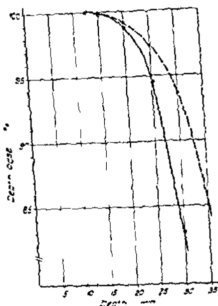


Fig 6 Central axis depth dose curves for 10 (——) and 13 (---) MeV electrons in the depth of interest.

tron densities amounted to only 7 per cent If the maximum deviations were taken into account, however, the greatest difference in density amounted to 30 per cent and the corresponding difference in electron density to 18 per cent, values which in fact partly explain the dispersion of absorbed dose found in the previous report

The complex chemical composition of sternum, ribs and costal cartilage makes it difficult to calculate the electron content for these compounds ICRU (1972) assumes for muscle tissue and compact bone the elementary composition given in Table 6 The electron content in these compounds were calculated and compared with the measured values in Table 5 for intercostal muscle tissue and rib bone. The results appear in Table 6 The values for muscle tissue agree closely, while the electron content of rib is 5 5 per cent less than that of compact bone This is reasonable because only a thin shell of compact bone surrounds the spongy parts of rib

Clinical considerations In the irradiation of the lymph glands along the internal thoracic vessels the target volume includes intercostal soft tissue, rib bone, costal cartilage and the sternum Internal mammary lymph nodes may be covered in part by costal cartilage especially in the first and second intercostal spaces (DAHL-IVERSEN 1951) URBAN (1959) reported the incidence of internal mammary lymph nodes to be 91 per cent at the first intercostal space, 89 per cent at the second, 75 per cent at the third, 53 per cent at the fourth and 13 per cent at the fifth

Within and adjacent to the target volume there are organs and tissues in which high doses of radiation may produce deleterious changes During left-sided irradiation the anterior part of the pericardium, parts of the anterior wall of the right ven-

Table 6

Calculated and measured electron content in various tissue compounds

Tissue	Electron content $g^{-1} \times 10^{-23}$
Muscle*, calculated	3 31
Intercostal muscle, measured	3 30
Bone**, calculated	3 19
Rib bone measured	3 02

Composition in per cent
* 10 2 H, 12 3 C, 3 5 N, 72 9 O, 0 08 Na, 0 2 Mg 0 2 P, 0 5 S, 0 3 K
** 6 4 H, 27 8 C, 2 7 N, 41 0 O, 0 2 Mg 7 0 P, 0 2 S, 14 7 Ca

influence on the dose distribution when the heterogeneities consist of objects with small cross-sectional areas, for example between 0 5 cm × 1 5 cm and 1 cm × 2 cm Ribs and costal cartilage constitute structures of small cross-sectional areas Accordingly, scatter effects should be considered Two adjacent ribs will for instance scatter electrons into the interstice in between, thus causing superimposed energy deposition This will result in alternating high and low dose regions in the chest wall BREITLING (1963) has demonstrated this effect in a model experiment using 16 2 MeV electrons The effect would be still more marked for lower energies as the scatter angle is strongly dependent on the electron energy In the investigation of the absorbed dose distribution behind specimens of the chest wall by TLD measurements (RAGNHULT et coll 1972) it was found that at the electron energy of 10 MeV the variation was ±10 per cent and at 13 MeV it was reduced to ±5 per cent It was suggested that the great dispersion of the dose could be explained by the influence of scattering effects occurring when the high-energy electrons interacted with the different components of the multi-structured chest wall In order to find experimental evidence for the magnitude of the effect, the electron densities in the different tissue materials were determined After correction of an error in the previous report (unfortunately the electron content for costal cartilage was over-estimated in the report of 1972, instead of $3\ 30 \times 10^{23}$ it should be $3\ 15 \times 10^{23}\ g^{-1}$), it was found that the greatest difference in mean values of electron densities for various types of tissue existed between rib bone and fatty tissue and that it could be expected to exceed 8 but not 16 per cent The most marked discontinuity existed at the interfaces between rib bone and intercostal soft tissue of muscles and interlaced fat The results given in Table 5 are plotted in Fig 5 and normalized to intercostal soft tissue In the same diagram the relative densities are also plotted It was found that the mean densities of the different types of tissue varied by 17 per cent, while the variation in mean elec-

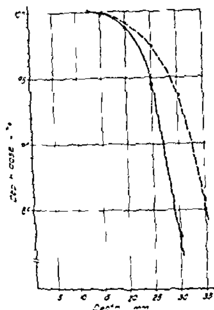


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Table 7

Reduction of relative depth doses in regions beyond heterogeneities Calculations are made for a depth of 28 mm using formula (7) The thicknesses and relative electron densities were maximum values (The value for sternum of specimen I was excluded)

Heterogeneity	Relative electron density	Maximal thickness mm	Reduction of depth dose (per cent)	
			10 MeV	13 MeV
Rib bone	1 17	6	2 6	0 8
Costal cartilage	1 06	10	1 6	0 4
Sternum	*1 05*	14	1 9	0 5

tricle and the left coronary artery will fall within or close to the target volume The situation is somewhat more favourable in right-sided irradiation In both cases the lungs will be close to the margin of the target volume In view of the proximity of these critical organs and the superficial position of the lymph glands, the use of electron radiation with a very limited depth of penetration is advisable

In clinical practice a limited overdosage in small regions is considered to be of little significance for the radiation effect Thus, the high dose regions caused by scattered electrons may be neglected It is, however, essential for successful therapy that no point within the target volume receives a lower absorbed dose than prescribed and, consequently, the reduction of absorbed dose beneath heterogeneities should be considered in treatment planning

The thickness of the chest wall, in the parasternal region after Halsted's operation, has, in the present investigation been determined to be less than or equal to 30 mm and the mean depth of the lymph glands 20 mm with a maximum deviation of ± 8 mm Fig 6 gives the relevant parts of the central depth dose curves for 10 and 13 MeV electron radiation from a BBC betatron (Asklepitron 35) measured in a polystyrene phantom The energies were determined as recommended by the Nordic Association of Clinical Physics (1972) Polystyrene has a density of 1 04 g cm^{-3} and an electron density of 0 338 10^{21} cm^{-3}, values which are very similar to the corresponding ones for soft tissue

Considering a lymph gland at the depth of d mm situated beneath a heterogeneity with the thickness t mm, an effective depth DE could be calculated from the formula

$$DE = d + (r - 1) \times t \qquad (7)$$

where r is the ratio of electron densities for heterogeneity and intercostal soft tissue This method of calculation does not allow for the effects of scattered electrons and should be used for estimation of the absorbed dose at a depth beyond the heterogeneity (BOONE et coll 1969)

The expression (7) and the central depth dose curves in Fig 6 were used for the determination of the reduction of relative depth doses given in Table 7 Here are

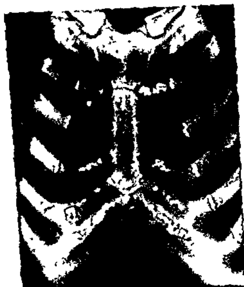


Fig 7 Tissue block of the anterior thoracic wall

considered the most difficult cases found in this investigation, viz. glands at the depth of 28 mm, positioned beyond heterogeneities of maximal thickness and maximal electron densities The effective depths DE differ from the real depth by 1 mm for rib bone and less in the other cases The reduction of relative depth dose is maximally 2 6 per cent, which occurs for rib bone This reduction is too small to need consideration in clinical practice and 10 MeV electrons can thus be used in treatment of the mammary glands, though a somewhat higher energy should have the advantage of reduced scattering effects For energies higher than 13 MeV, however, parts of the lung tissue and the myocardium would receive more than 90 per cent relative absorbed dose Thus, 13 MeV was considered as the highest recommendable energy in the cases where underlying critical tissue was to be spared

Conclusions The electron densities of different types of tissue in 8 specimens of the anterior chest wall of human beings were determined The mean electron densities of the different types of tissue varied by 7 per cent, while the maximum deviation was 18 per cent Using the determined values it was estimated that underdosage beneath heterogeneities could be limited to 2 6 per cent of the relative depth dose if electron energies not lower than 10 MeV were used Considering critical tissues underlying the target volume, 13 MeV was recommended as an upper limit of energy Thus, it was concluded that electron radiation in the energy range of 10 to 13 MeV could be used for treating the internal mammary glands

Attenuation of 10 and 13 MeV electrons in the anterior chest wall

Attenuation of high en . . .

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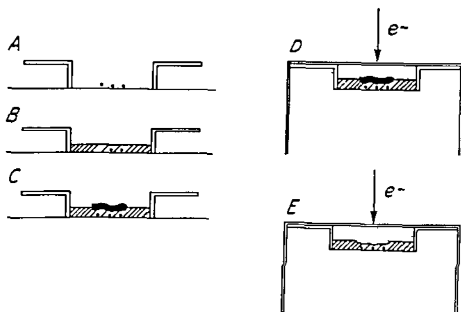


Fig 8 Schematic principle of the experimental method A Catheters and perspex frame placed horizontally on a level surface B Molten paraffin wax covers the catheters C The specimen pressed down over the catheters in the paraffin D Perspex frame with specimen and catheters fixed in the set paraffin lowered vertically into a water phantom and fixed to the front wall of the phantom Before irradiation the catheters are filled with probes containing TLD dosimeters E Repeated irradiation with the specimen removed and new probes introduced into the catheters

trons in bone and water was determined by HATTORI & KITABATAKE (1968) who found that the difference was negligible for the energy range 16 to 31 MeV BOONE et coll (1967, 1969) estimated the attenuation of electrons in the anterior chest wall of dogs using energies from 6 to 15 MeV They concluded that the distribution of absorbed dose was significantly perturbed when electrons with energies between 6 and 9 MeV were used but that the reduction of absorbed dose beneath the inner aspect of the chest wall between 12 and 15 MeV was negligible

To determine the reduction of absorbed dose behind fresh specimens of ribs costal cartilages and sternum (Fig 7) an experimental technique was developed enabling dosimeters to be placed immediately under the specimens in regions in which low absorbed dose was to be expected and little influence of electrons scattered from the surroundings

Methods

Measurements of absorbed dose were performed by means of thermoluminescent dosimetry Small LiF teflon dosimeters (cylinders 6 mm × 1 mm) were used inserted into teflon tubes (wall thickness 0 25 mm) The instrument and the measuring technique used have been described previously (LINDSKOUG et coll 1967 JOHANSSON et coll 1969)

Two tissue blocks of the anterior thoracic wall were used After removal of the soft tissues from the surfaces of the specimens the densities of the specimens were determined

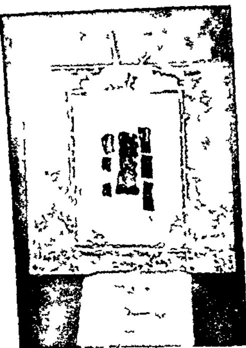


Fig 9 Specimen mounted in paraffin surrounded by a perspex frame Catheters emerging behind the upper edge of the perspex frame

Catheters made of teflon were fixed in a perspex frame and molten paraffin wax was poured over them to a thickness of approximately 15 mm The experimental set up is schematically illustrated in Fig 8 Specimens of the dissected tissue block were gently pressed into the paraffin and positioned right over the catheters (Fig 9) The dosimeters were surrounded by paraffin ($C_{16}H_{34}$) which has an electron density about 4 per cent lower than that of water Thus electron back and side scatter contribution from the paraffin to the dosimeters should be very small compared with the corresponding scatter contribution from intercostal soft tissue which has an electron density 1 024 times higher than water The frame with the paraffin sheet specimens and catheters was placed vertically in a water phantom (Fig 10) and fixed to the 5 mm thick polystyrene wall Probes containing LiF dosimeters were introduced into the catheters and irradiation was performed by means of a BBC betatron (Asklepitron 35) The absorbed dose to water was always 100 rad at the depth of the dose maximum The specimens were then carefully removed from the paraffin sheet without changing the position of the perspex frame and irradiation repeated using new probes in the catheters The geometry was thus unchanged but water was substituted for the tissue block The depths of the structures and dosimeters were as follows

From front surface of phantom to front surface of specimen 6–18 mm from back surface of specimen to point of measurement 2 5 mm and total depth of measurement 20–26 mm

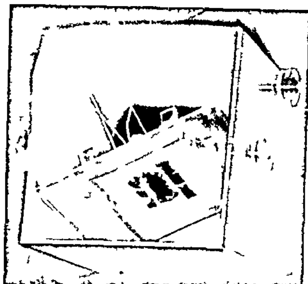


Fig 10



Fig 11

Fig 10 Perspex frame with specimen and catheters in an unfilled water phantom

Fig 11 Mounted specimen Sternum and manubrium ribs and costal cartilage Catheters filled with indicator probes

The paraffin sheet with various specimens and probes containing indicators of copper inserted into the catheters appear in Fig 11

Result

The results of the determinations are given in Table 8 The three columns to the left give information about the type of specimen and the number of dosimeters used, the mean dimension of the specimen in the direction of radiation, the mean density of the different specimens and their respective standard deviations The dimensions of the specimens are given for the sections lying directly in front of each dosimeter The next three columns represent the absorbed doses and the relative absorbed doses determined for an electron energy of 10 MeV The three columns to the far right show the corresponding results for 13 MeV electrons The relative absorbed dose is given for the heterogeneous case (specimen) in percentage of the homogeneous case (water) The overall mean values for the different specimens appear in Table 9

It is evident that the reduction of absorbed dose for the energy of 10 MeV did not in any case exceed 3 per cent For the energy of 13 MeV it seems doubtful whether reduction of absorbed dose is significant

The tissue blocks used were taken from bodies of rather high age, with calcium

Table 8

Results for two tissue blocks (A and B) irradiated with 10 and 13 MeV electrons. Relative absorbed dose calculated for the heterogeneous case (specimens) in percentage of the homogeneous case (water). Number of measurement points (within brackets) and standard deviations (SD) are given on the second lines

Material	Dimension in the direction of radiation (mm)	Density g cm^{-3}	10 MeV Absorbed dose Water (rad)	10 MeV Absorbed dose Specimen (rad)	Spec / water Rel dose (per cent)	13 MeV Absorbed dose Water (rad)	13 MeV Absorbed dose Specimen (rad)	Spec / water Rel dose (per cent)
A								
Rib bone	3.7	1.22	98.3	95.8	97.5	108.5	105.5	97.2
SD (6)	0.8		1.0	2.0	1.7	1.0	0.5	1.0
Sternum	10.9	1.13	98.8	95.8	97.0	106.0	108.9	102.9
SD (10)	2.1		4.5	4.7	2.5	5.4	4.7	4.5
Costal cartilage	5.0	1.10	97.2	95.8	98.5	100.6	103.6	103.0
SD (5)	0.8		2.6	4.6	2.4	3.3	3.8	2.6
B								
Rib bone	4.8	1.13	72.8	73.7	101.1	88.8	91.7	103.2
SD (6)	0.8		2.8	3.8	2.4	1.7	3.0	1.9
Sternum	10.5	1.08	80.4	79.8	99.3	91.7	89.4	97.6
SD (12)	1.2		4.1	4.3	2.6	2.8	1.8	1.9
Costal cartilage	8.6	1.19	66.2	65.6	99.1	86.0	84.0	98.0
SD (5)	1.1		1.8	1.8	2.9	5.5	0.7	5.8

salts already deposited in the cartilage matrix. Fig. 7 might give the impression that the calcified areas constitute important heterogeneities inside the costal cartilage. The film was, however, exposed with 40 kVp, which is a quality where the attenuation of photons is strongly dependent upon the atomic number (Z) of the irradiated material. Thus the calcified areas appear with high contrast in the image. The attenuation of electrons will, however, mainly depend upon electron density of the material but a significant dose reduction should still be expected beneath a calcified area. The dosimeters are too large, however, to allow detailed determination of the dose distribution in the regions beneath these small calcium deposits.

Discussion

Measurements in vivo will always be influenced by variations in field flatness. With the present experimental set-up variations in field flatness will be the same with and without specimen as they are irradiated with short intervals

Table 9

Mean values for the two tissue blocks (A + B), and overall mean values

Material	Dimension in the direction of radiation (mm)	Density g cm^{-3}	10 MeV Absorbed dose Water (rad)	10 MeV Absorbed dose Specimen (rad)	Spec / water Rel dose (per cent)	13 MeV Absorbed dose Water (rad)	13 MeV Absorbed dose Specimen (rad)	Spec / water Rel dose (per cent)
Rib bone	4 3	1 19	86	85	99 3	99	99	100 2
SD (12)	1 0		13	12	2 7	10	8	3 4
Sternum	10 7	1 11	89	87	98 2	98	98	100 0
SD (22)	1 6		10	9	2 8	8	10	4 2
Costal cartilage	6 9	1 08	82	81	98 8	93	94	100 5
SD (10)	2 0		16	16	2 5	9	11	5 0
Overall mean values	8 1	1 13	86	85	98 7	97	97	100 2
SD (44)	3 2		13	12	2 7	9	10	4 1

It may be concluded that the attenuation of electron radiation in the energy range 10 to 13 MeV in rib, costal cartilage and sternum does not differ significantly from that in soft tissue The highest reduction of absorbed dose compared with the reduction in water was found to be 3 per cent which was valid for ribs This was within the limits of precision for the TLD measurements (JOHANSSON et coll) The results confirm the conclusion that electron radiation in the energy range of 10 to 13 MeV can be utilized for irradiation of internal mammary lymph nodes without risk of underdosage

Acknowledgements

The authors are particularly indebted to Prof Holger Skoldborn for valuable discussion and encouragement throughout the investigation For constructive criticism we thank Prof C Carlsson This investigation has been partly financed by funds made available by the Swedish Cancer Society and partly by funds provided by the Faculty of Medicine, University of Gothenburg, Sweden

SUMMARY

The density (g cm^{-3}) and electron density (cm^{-3}) of material from the anterior chest wall was determined On the average, the difference in density between rib bone and intercostal soft tissue amounted to 17 per cent, while the difference in electron density was 7 per cent The attenuation of high-energy electrons in specimens of rib bone, costal cartilage and sternum was determined by an experimental technique, using dosimeters of TLD material The results of determinations of attenuation of 10 and 13 MeV electrons in fresh specimens are presented It is concluded that electron radiation in the energy range of 10 to 13 MeV can be utilized for irradiation of lymph glands along the internal thoracic vessels without risk of underdosage

ZUSAMMENFASSUNG

Die Dichte (g cm⁻³) und Elektronendichte (cm⁻³) der Gewebe der vorderen Brustwand wurden bestimmt Im Durchschnitt betrug die Differenz in der Dichte zwischen dem Rippenknochen und dem intercostalen Weichteilgewebe 17 Prozent, während die Differenz in der Elektronendichte 7 Prozent betrug Die Abnahme der hochenergetischen Elektronen in Proben von Rippenknochen, Rippenknorpel und Brustbein wurde durch einen experimentellen Test unter Verwendung von Dosimetern aus TLD Material bestimmt Die Ergebnisse der Bestimmungen uber die Abnahme von 10 und 13 MeV Elektronen in frischen Geweben werden gegeben Die Verfasser schliessen daraus, dass die Elektronenbestrahlung im Energiebereich zwischen 10 und 13 MeV zur Bestrahlung der Lymphknoten langs der inneren Thoraxgefasse ohne Risiko einer Unterdosierung verwendet werden kann

RÉSUMÉ

Les auteurs ont mesuré la densité (g cm⁻³) et la densite électronique (cm⁻³) de tissus de la paroi thoracique anterieure En moyenne la difference de densite entre l'os costal et les tissus mous inter-costaux est de 17%, alors que la difference de densité electronique est de 7% L atténuation des electrons de haute energie dans des fragments d'os costal, de cartilage costal et de sternum a ete déterminee par un test expérimental utilisant des dosimétres en matériaux pour TLD (materiaux pour dosimétrie par thermoluminescence) Les auteurs presentent les resultats des mesures d atténuation d electrons de 10 et de 13 MeV pour des fragments anatomiques frais Ils concluent que le rayonnement electronique dans le domaine d energie entre 10 et 13 MeV peut être utilise pour l irradiation de ganglions lymphatiques le long des vaisseaux thoraciques internes sans risque de sous-dosage

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METASTASIS FROM AN UNKNOWN TUMOUR

INGER DISSING

The diagnosis of metastasis from an unknown primary tumour always constitutes an unsatisfactory basis for treatment and usually a fatal outcome is inevitable, unless the primary tumour is found Nevertheless some patients survive for a long time after the treatment of metastases even without the primary tumour being detected

Only a few authors have discussed the treatment of metastases in general (HOLMES & FOUTS 1970, AGLIOZZO & REINGOLD 1967, GEWANTER et coll 1943) Only HOLMES & FOUTS have presented a clinical material but unfortunately they make no mention of treatment

Nearly all previous authors have restricted themselves to metastases in the lymph nodes and mainly in the neck (BARRIE et coll 1970, COMESS et coll 1957, HENDRICH 1967, JESSE et coll 1966 1973, MARTIN & MORFIT 1944, PROBERT 1970) Their results are much better than those of HOLMES & FOUTS and this also applies to the present material consisting of metastases of all sites

The purpose of this investigation was to find out if any relation existed between the nature of the malignancy and the survival rate

Material

During the period 1955 to 1965, 228 patients out of a total of 45 000 consecutive patients were treated under the diagnosis metastasis from unknown primary tumour Thirteen, later found to have systemic disease, were excluded One patient was

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Table 1

Microscopic diagnosis of metastases by location

Diagnosis	Location of metastases							No of patients
	Cervical lymph nodes			Axill lymph nodes	Ing lymph nodes	Bones	Organs or soft tissue	
	Upper	Middle	Lower					
Solid carc	12	7	14	4	2	6	10	39
Squamous-cell carc	11	7	2	2	1	1	0	21
Anapl carc	5	2	4	0	3	2	4	17
Adenocarc	3	0	2	0	2	2	5	13
Malignant melanoma	0	0	2	0	2	0	3	5
Others	5	2	2	2	1	4	6	17
No of metastases	36	18	26	8	11	15	28	

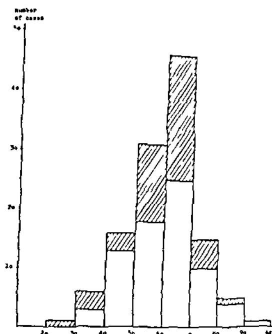
cases the slides were reviewed by J Clemmesen (Senior pathologist, Finsen Institute, Copenhagen)

Location The metastases had developed in practically all parts of the body, but in 68 patients (56 per cent) they were located in the cervical lymph nodes SINNER (1959) found that 78 per cent of the metastases in his material involved the lymph nodes in the neck, and most previous authors have been concerned solely with metastases in this location

In 29 of the patients with metastases in the cervical lymph nodes, 23 with lesions on the left side of the neck and 6 on the right, a primary tumour was later disclosed Sixteen primary tumours were located above the clavicle, 13 below The primary sites above the clavicle were rhino-pharynx, nasal cavity, oral cavity, root of the tongue, tonsils, larynx, parotid gland and thyroid gland, while the primary sites below the clavicle were oesophagus, lungs, pancreas, colon, liver, common bile duct, kidneys, bladder, and a malignant melanoma in the plantar skin

Microscopy The most common microscopic diagnoses were solid carcinoma and squamous-cell carcinoma (Table 1), the rest comprised indeterminate malignant tumour, mucoid tumour, metastases resembling thyroid tissue and hypernephroma, but with nothing abnormal found in the thyroid gland or kidneys As could be expected, most of the metastases of the squamous cell type were found in the cervical lymph nodes, and the silent primary tumour later found was most often in the upper respiratory or digestive tract

Treatment As the metastases in this material were localized in many different regions, no special therapeutic schedule was used Before 1962 the majority were



The distribution according to age and sex
[men symbol] = men, [women symbol] = women

excluded on the basis of the principles of MARTIN & MORFIT, having a squamous-cell carcinoma within a branchial cyst After the material had been restricted to patients in whom no primary tumour was found within the first 6 months after treatment of the metastasis, 121 patients remained All were included in a follow-up in December 1973

The age distribution and sex ratio are similar to those found in other materials, 74 patients being men and 47 women, with the age peak between 50 and 70 (Figure)

In about half the cases, a painless mass made the patient seek medical advice, while tenderness, pain or functional disturbances were responsible in one third The history ranged from a few days to several years, mean 7 7 months

PROBERT suggested that the longer the history, the better the prognosis In the present material, however, the 5-year survival rate after a history of less than 6 months was 21 per cent, after more than 6 months 13 per cent, the 10-year rate was 11 and 7 per cent, respectively Thus, PROBERT's suggestion was not confirmed

If examinations of the most probable sites for a primary tumour were negative, the metastasis was excised totally when possible, or a drill biopsy was performed

The diagnosis of metastasis was verified microscopically in all but 9 cases in whom no biopsy was performed Six of these patients had osteolytic bone metastases One patient, subjected to laparotomy, had gross metastases in the liver, mesentery, and abdominal lymph nodes Another had a mass in the mediastinum with nerve palsy and oesophageal stenosis The last patient received preoperative irradiation to the neck; at operation no tumour tissue was found although he later developed several further metastases and died All microscopic reports have been reviewed In doubtful

Table 3

Group 1 8 patients still alive without detection of a primary tumour

Age	Sex	Microscopic diagnosis	Metastases (region)	Treatment	Recurrence after treatment	Survival after last treatment (years)
53	M	Adenopap carc	Cerv lphn	Excision + 180 kV 3 300 R/23d	None	14
58	M	Melanoma	Ing lphn	Radical ing dissection	None	13
50	F	Solic carc	Cerv lphn	Excision + 250 kV 4 100 R/30d	None	11
30	F	Anapl carc	Ing lphn	Excision + ^{60}Co 5 000 rad/25d	None	8
56	F	Squam.-cell carc	Cerv lphn	Excision + ^{60}Co 6 300 rad/58d	None	8
56	M	Squam -cell carc	Axill lphn	Axillary dissection + 400 kV 3 030 R/19d	Right lung 9 years later	5
70	F	Anapl carc	Thoracic subcut	Excision	Cerv lphn 1 year later	9
55	F	Solid carc	Pretracheal lphn	Excision + ^{60}Co 5 700 rad/44d	Cerv lphn 2 years later	6

Group 1 The first group consisted of 8 patients (6 6 per cent) who were still alive without a primary tumour being detected (Table 3) Five had no evidence of malignancy since the first treatment Three had received treatment for a second metastasis and were then without any sign of tumour

Within this group the microscopic diagnoses varied widely, and so did the locations of the metastases Three patients had received orthovoltage roentgen irradiation with tumour doses between 3 030 R/19 days and 4 100 R/30 days, 3 were irradiated with ^{60}Co with tumour doses between 5000 rad/25 days and 6 300 rad/58 days The seventh patient had a radical inguinal lymph node dissection, and the eighth an excision only Of the 3 patients with recurrences, 2 developed the second metastasis outside the primarily [illegible] neck dissectic[illegible] oped in a pr[illegible] node on the left side and the second in the lymph nodes on the right side of the neck, partly inside the initially treated region Radical neck dissection was then performed All the patients in this group were surviving 8 to 14 years after the primary treatment

Group 2 In 19 cases (15 7 per cent), the primary tumour was found while the patient was still alive Two were still alive and well after 14 years

Table 2

Present material

Group		Males	Females	Total
1	Living without a primary tumour being disclosed	3	5	8
2	Primary tumour detected during life	14	5	19
3	Primary tumour detected at autopsy	16	11	27
4	Died without a primary tumour being detected at autopsy			
	No tumour tissue	2	2	4
	Died of tumour	14	9	23
5	Died without a primary tumour being detected, no autopsy			
	No clinical evidence of tumour	2	1	3
	Died of tumour	23	14	37
Total		74	47	121

treated with orthovoltage roentgen irradiation using different field sizes, in most cases including the neighbouring lymph nodes Only a few were treated with ^{60}Co irradiation and a field size of up to 8 cm × 6 cm and a FSD of 20 cm After 1962 nearly all patients received ^{60}Co irradiation including all the neighbouring lymph nodes

Seventy-six patients were treated with orthovoltage irradiation and 23 with ^{60}Co The calculated tumour doses were less than 2 500 R in 32 cases, between 2 500 and 4 500 R in 36 cases, between 4 500 and 6 500 R in 29 cases, and more than 6 500 R in 2 cases It has not been possible to estimate the CRE (Cumulative Radiation Effect) for all treatments, and the calculated CRE values bore no relationship to the survival rate

The remaining patients received radiation therapy after biopsy or excision of the metastasis, except one who was irradiated pre-operatively and 3 who were irradiated following a block dissection of the neck

The metastases were excised totally in 10 patients as the first treatment, and radical lymph node dissection was performed in 2 patients Four patients were not treated at all and 6 patients with advanced disease received chemo-therapy with a single drug endoxan, erasol, or Bayer E 39

Sixty-nine of the patients died between 6 and 18 months after the first treatment but 10 were still alive in December 1973, 8 without the primary tumour being detected, and 2 after their primary tumour had been detected and treated Altogether, the primary tumour was disclosed during life or at autopsy in 46 patients The entire material may then be grouped as appears in Table 2 Forty patients died without the primary tumour being detected and no autopsy was performed

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The remaining patients received radiation therapy after biopsy or excision of the metastasis, except one who was irradiated pre-operatively and 3 who were irradiated following a block dissection of the neck

The metastases were excised totally in 10 patients as the first treatment, and radical lymph node dissection was performed in 2 patients Four patients were not treated at all and 6 patients with advanced disease received chemo-therapy with a single drug endoxan, erasol, or Bayer E 39

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Table 5

Crude survival after treatment of metastases

Group	3 years		5 years		10 years	
	Recurrence	No recurrence	Recurrence	No recurrence	Recurrence	No recurrence
1		8		8		5
2	7	3	5	2	2	2
3	3	3	1			
4 a		2		2		1
4 b		1				
5		2				
5	2	4	1	2	1	
Total	12	23	7	14	3	8
Per cent	28 9		17 4		9 1	

were excised in 3 patients and radical neck dissection was performed in 2 In 13 cases curative treatment of the primary tumour was possible in spite of the previous treatment In 6 cases the primary tumour was too widespread for radical treatment Three patients underwent radical operation and 9 had curative irradiation One patient died of heart failure before any treatment had been instituted

Group 3 In 27 cases (22 3 per cent) the primary tumour was not detected until *post mortem* In other words, the total number of primary tumours detected, either *during life* or at autopsy, was 46 (38 per cent) The longest survivals from the first treatment were 63 and 57 months Thirteen of the 27 cases of this group had metastases in the cervical lymph nodes, in 8 of these the primary tumours were located below the clavicle lung 4, kidney 1, liver 1, common bile duct 1, and plantar skin 1 The primary tumours above the clavicle were located in rhinopharynx 1, tongue 1, larynx 1, and thyroid gland 2 In the cases with metastases outside the neck the primary tumours were located in lung 4, pleura 1, thyroid gland 1, kidney 3, gastrointestinal tract 2, ovary 1, vagina 1, and testis 1 Fifteen of the patients were treated with orthovoltage irradiation with tumour doses between 600 R/21 days and 4 400 R 29 days, 3 had ^{60}Co irradiation with doses between 1 230 rad/38 days and 6 000 rad 34 days, while 3 patients were not treated at all One patient underwent radical neck dissection, 3 merely had excision of the metastasis, and 2 received chemotherapy In 2 cases with a tentative microscopic diagnosis of reticulosarcoma, the diagnosis was changed at autopsy In one of these two, lymph node recurrences had been biopsied, yielding different microscopic diagnoses, but finally autopsy established the diagnosis of *seminoma* All the earlier slides were revised and proved compatible with the diagnosis of seminoma

Table 4

Died without recurrence or evidence of primary tumour at autopsy in group 4 a

Age	Sex	Microscopic diagnosis	Region	Treatment	Survival (years)	Cause of death
58	M	Carcinoma	Cerv lphn	180 kV 3 240 R/44d	11	Cardiac failure and uraemia
70	F	Malignant cells	Cerv lphn	180 kV 1 300 R/28d	8	Cerebral haemorrhage
66	M	Solid anapl carc	Cerv lphn	180 kV 1 770 R/40d	2	Hepatic abscess septicaemia
68	F	Solid anapl carc	Cerv lphn	250 kV 5 200 R/39d	1	Cirrhosis and hepatic coma

Female, aged 64 In 1959 squamous-cell carcinoma in cervical lymph node on the left excision followed by irradiation 180 kV 4 800 R/28 d In 1963 tumour in the left tonsil and another left lymph node metastasis outside the first field, microscopy, squamous-cell carcinoma, ^{60}Co irradiation 6 217 rad/56 d No recurrence at 10 years

Female, aged 68 In 1959 squamous-cell carcinoma in cervical lymph node on the left, excision In 1967 carcinoma of the uterine cervix, squamous-cell carcinoma of the left tonsil and in a lymph node on the left side of the neck ^{60}Co irradiation 6 600 rad/60 d No recurrence at 6 years

One case died one year after ^{60}Co irradiation, 5 000 rad/37 days, of a primary tumour in the larynx, 3 years after irradiation, 180 kV, 3 700 R/27 days, of a squamous-cell carcinoma in a cervical lymph node on the left side of the neck He died of melaena from a gastric ulcer, with no evidence of tumour at autopsy The remainder of the patients died of their tumours a few weeks to 10 years after treatment of the primary tumour with a mean survival of 20 months The longest interval between the treatment of a metastasis and the diagnosis of the primary tumour was 10 years, in this case, another 3 metastases of the parotid tumour had occurred in the neck and mediastinum during that period Of the 19 patients, 16 had their metastases in the cervical lymph nodes and of these, 5 had their primary tumour below the clavicle lung, oesophagus, pancreas, colon, and bladder The location of the primary tumours above the clavicle were tonsils 4, rhinopharynx 1, nasal cavity 1, tongue 1, parotid gland 1, larynx 3 Skeletal metastases from a primary tumour in the lung were found in 1 case and from renal tumours in 2 cases The metastases were treated in 9 cases with orthovoltage irradiation with tumour doses between 1 200 R/14 days and 6 200 R/41 days, and in 5 cases with ^{60}Co irradiation with doses between 4 004 rad/23 days and 6 700 rad/51 days The lymph nodes

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5	2	4	1	2	1	
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Table 6

Crude survival of 88 patients according to size of palpable metastasis

Survival (years)	Size of metastasis	No of cases	Primary tumour found	No primary tumour found	Per cent
<3	<20 cm²	29	16	13	58
	>20 cm²	30	6	24	79
>3	<20 cm²	21	7	14	42
	>20 cm²	8	4	4	21
>5	<20 cm²	14	4	10	28
	>20 cm²	3	1	2	8

Group 4 This group of 27 patients was sub divided into (a) cases with no tumour tissue at autopsy (4 patients), and (b) cases with tumour tissue at autopsy, but with no apparent primary tumour (23 patients) (Table 4) All but one of the group (b) cases had died of their malignancy within 18 months This one lived for 4 years with many recurrences of adenocarcinoma in the abdominal wall before dying with generalized metastases

Group 5 No autopsy had been performed on 40 patients in whom no primary tumour was found during life Three died of cardiovascular failure without clinical signs of tumour 2, 3, and 4 years, respectively, after treatment for metastases The remainder of this group died of their tumour, but in 2 cases 10 and 6 years elapsed between the first metastases and the recurrences Twenty-nine of them died less than one year after treatment of the first metastases

Survival Thirty-five patients survived for 3 years (a crude survival rate of 28 9 per cent, Table 5), in 23 of these no recurrences developed The 5-year crude survival was 17 4 per cent, and of this group 14 patients developed no recurrences, 10 of them had their metastases in cervical lymph nodes Eleven patients, constituting 9 1 per cent of the material, lived for 10 years or more (up to 14 years) At the time of follow up (December 1973) no recurrences were present in 8, including 5 whose metastases had been in the cervical lymph nodes

Eighth-eight patients had measurable metastases when first treated The remainder had either had their metastases totally removed, destruction in bone, or tumour tissue in the pleura Fifty patients had metastases measuring less than 20 cm² (Table 6), 21 of these (42 per cent) lived for more than 3 years On the other hand, only 8 (21 per cent) of the 38 patients with metastases exceeding 20 cm² lived for more than 3 years, 28 per cent with metastases of less than 20 cm² lived for more than 5 years, while 8 per cent of those with metastases exceeding 20 cm² lived for more than 5 years Thus, the prognosis does seem to be related to the size of the metastases, as suggested by [6] ROBERT

Discussion

The improvements in diagnostic techniques over the years have not lessened the problems of the metastasis from an unknown primary tumour (HOLMES & FOUTS) Destruction in a bone or a lump in an organ is not ordinarily a diagnostic problem but a palpable lymph node may be normal or it may be metastatic, a painful lymph node may be infected or it may be metastatic and affected with secondary infection Thus, an exact microscopic diagnosis is necessary and also important for excluding systemic diseases which may sometimes be diagnosed initially as anaplastic carcinoma Some authors do not exclude these cases, even though the exact nature is revealed later (BARRIE et coll, PROBERT) In the present material all such cases were excluded

The reported treatment of metastases from an unknown primary tumour has varied widely, but most often it consists of irradiation, alone or combined with operation By irradiation of extensive fields, covering all neighbouring lymph nodes, the unknown primary tumour may be treated as well This may be the reason why some patients survive for a long time without their primary tumour being detected

Among the explanations for not detecting the primary tumour HOLMES & FOUTS mentioned a primary tumour too tiny for diagnostic examinations, too small to be detected at autopsy, no autopsy, early malignant melanomas or endometrial adenocarcinomas destroyed without microscopy or spontaneous regression (EVERSON & COLE 1966) As an example of a tiny primary tumour GIKAS et coll (1967) mentioned a case in which a primary tumour in the thyroid gland, measuring 0 6 mm × 0 3mm × 0 2 mm had given a metastasis in a cervical lymph node

The reported survival rates have varied widely, but so have the materials The material of HOLMES & FOUTS included similar metastases as in the present one, but their crude survival rates for 3, 5 and 10 years were 7 8, 5 1 and 3 3 per cent, respectively while the corresponding survival rates in the present material are 28 9, 17 4 and 9 1 per cent

Others dealing only with lymph node metastases in the neck, have presented much higher crude survival rates BARRIE et coll found a 30 per cent 3 year, a 25 per cent 5 year and a 15 per cent 10-year survival, but they had excluded all cases of anaplastic carcinoma COMESS et coll stated that 12 4 per cent of their patients were alive at 11 years without having had the primary tumour detected HENDRICH (1967) found 17 3 per cent surviving at 3 years without any sign of tumour while JESSE et coll (1973) had 48 per cent surviving at 3 years However, they had excluded advanced localized tumours as well as disseminated tumours MARCHETTA et coll (1963) found a 30 per cent 4-year survival and PROBERT an 8 per cent 3 year survival In the present material the survival rates for patients with metastases only to the cervical lymph nodes were 30 6 per cent at 3 years, 19 per cent at 5 years and 12 4 per cent at 10 years

The size of the metastasis plays an important prognostic role, as apparent from the present material and as pointed out by PROBERT A large metastasis has either been

growing through a long time or contains fast-growing, highly malignant tumour tissue, factors spelling a poor prognosis. PROBERT suggested that anaplastic carcinoma has a better prognosis than other types, and HOLMES & FOUTS found that 8 of their anaplastic cases survived for 5 years or longer. In the present material 17 patients (14 per cent) had microscopically proven anaplastic carcinoma. Among the 5-year survivors they constitute 19 per cent and among the 10-year survivors 27.3 per cent.

Conclusion

Since 14 out of 121 patients survived for more than 5 years after treatment of their metastases without any primary tumour being detected, it seems justifiable to treat these patients by curative measures. It is also advisable to continue to search for the *primary tumour, as it may be curable, even when found several years later.* The best treatment is difficult to decide, as the measures in the literature have varied and the treatment also must be appropriate to the site of the metastasis. The preferred treatment seems to be irradiation, sometimes combined with operation, and such treatment may by chance include the unknown primary tumour. In the present material, however, 5 of 12 patients having received only local surgery, survived for more than 5 years.

The metastasis should be removed totally to afford the best possible microscopic information. It has been suggested that anaplastic carcinoma has a better prognosis than other types, this cannot be disproved by the present findings. The site of the metastasis as well as the size is important and the best results are encountered among patients with metastases to the lymph nodes, especially in the neck, while metastases to organs and bones give a low survival rate.

SUMMARY

A total of 121 patients were treated under the diagnosis *metastasis from an unknown* primary tumour, 99 were irradiated. In 46 cases the primary tumour was detected from 6 months to 10 years after the primary treatment. The 3-year survival was 28.9 per cent, the 5-year 17.4 per cent and for 10 years or longer (up to 14 years) 9.1 per cent after the primary treatment. The prognosis is correlated to the size of the metastases, their site and also their microscopic appearances.

ZUSAMMENFASSUNG

Insgesamt 121 Patienten unter der Diagnose Metastase eines unbekannten Primartumors wurden behandelt, 99 wurden bestrahlt. Bei 46 Fallen wurde der Primartumor 6 Monate bis zu 10 Jahren nach der Primärbehandlung entdeckt. Die 3 Jahres Überlebensrate betrug 28,9 %, die 5 Jahres Überlebensrate 17,4 % und die fur 10 Jahre oder langer (bis zu 14 Jahren) 9,1 % nach der Primarbehandlung. Die Prognose ist zur Lage, der Grosse und dem mikroskopischen Bild der Metastase korreliert.

RÉSUMÉ

Un total de 121 malades ont été traités sous le diagnostic de métastase d'une tumeur primitive inconnue, 99 ont été irradiés. Dans 46 cas la tumeur primitive a été décelée entre

6 mois et 10 ans après le premier traitement Le taux de survie à 3 ans a été de 28,9%, a 5 ans de 17,4% et pour 10 ans ou plus (jusqu à 14 ans) de 9,1% après le premier traitement Le pronostic est en rapport avec la taille des metastases, leur localisation et leur aspect microscopique

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EN-BLOC IRRADIATION OF TUMOURS OF THE HEAD AND NECK AND THEIR LYMPHATICS

I Technique and dosimetry

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In the treatment of malignant tumours of the head and neck uncontrolled metastatic disease in the cervical lymph nodes has become a major cause of treatment failure, since with improvements in radiation technique the primary tumour is now more often cured

The topographic position of the cervical lymph nodes in health and disease has been demonstrated by FISCH (1968) In the normal cervical lymphogram the posterior border of the lymph node chain is superimposed upon the spinal processes of the cervical vertebrae and the nodes are thus situated posteriorly to the cervical spinal cord In case of metastatic node disease or after surgery they may be located still more posteriorly and then also the contralateral nodes may be filled

The frequency of different neck node involvements at presentation for different tumours of the head and neck has been demonstrated by FLETCHER et coll (1973) In their series the posterior cervical lymph nodes were most often involved when the primary tumour was located in the tonsillar fossa, base of the tongue, oropharyngeal walls nasopharynx and hypopharynx, but less often when the primary tumour was located in the oral tongue, floor of the mouth, retromolar trigone, anterior faucial pillar soft palate, or supraglottic larynx

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If it is desired to include in the target not only the primary tumour but also the lymphatics on both sides of the neck in the curative treatment of tumours of the head and neck, the cervial spinal cord presents a dilemma, since the absorbed dose often aimed at in the target equals or exceeds the cord tolerance In gross metastatic disease in the neck this is usually the case; in only microscopic deposits in the cervical lymph nodes a smaller absorbed dose may be sufficient However, subclinical disease may not always be the same as microscopic disease

Precise data on the radiation tolerance of the spinal cord are lacking It seems that several factors are of importance Such are the relative size of the irradiated volume (BODEN 1950, BERG & LINDGREN 1963), the condition of the vascular supply of the cord (ASSCHER & ANSON 1962), the total absorbed dose in the cord and the type of fractionation used Most reports indicate that the threshold value for radiation myelitis is of the order of 3 900 rad given over 4 weeks (BODEN, PALLIS et coll 1961, PHILLIPS & BUSCHKE 1969) The radiation sensitivity of the spinal cord seems to be time-dependant with a slope of the time-dose line of the order of 0 26 (LINDGREN 1958) to 0 21 (PALLIS et coll) Relatively large absorbed doses may then be tolerated if the treatment extends over a long period of time, provided that the absorbed dose at each fraction be not too large (ATKINS & TRETTER 1966, PHILLIPS & BUSCHKE) In the therapy of malignant lymphoma, this may be useful, but in the therapy of epithelial tumours, prolongation of total treatment time and number of fractions can not be used to the same extent

BAEKMARK (1975) reported on neurologic complications after irradiation of the cervical spinal cord in the treatment of malignant tumours of the head and neck Myelopathy was observed in 7 per cent of the patients Patients who also received chemotherapy with Vincristine had a higher frequency (30 per cent) of myelopathy Most of the patients with myelopathy had received a cord dose in the range 3 000 to 3 900 rad given with 1 000 rad per week, but some patients had received larger absorbed doses BAEKMARK stated that 'an attempt to avoid including the spinal cord in the irradiation involves a risk of underdosage of tumour-affected area, this has to be weighed against the risk of producing radiation myelitis'

If in the irradiation of malignant epithelial tumours in the region of the head and neck, lateral opposed ports are used to include the cervical lymph nodes, the ports have to be reduced towards the end of treatment to save the cord, and additional measures have to be taken to obtain optimum cure rate Such measures may be the addition of tangential fields to avoid the cord, boost therapy with electrons or implants, or surgery Alternatively may also from the very beginning a more complicated technique be used RUBIN & KELLER (1975) described different techniques used in laryngeal carcinoma, and reported for instance a technique with two posterior oblique fields with wedges and compensators to include the cervical nodes

The purpose of the present communication is to report a radiation technique for malignant tumours in the region of the head and neck which allows for en-bloc irradiation of the primary tumour and all cervical lymph nodes from the tip of the

mastoid down including those in the supraclavicular fossa as well as the retropharyngeal nodes, without exceeding the tolerance of the spinal cord In this Department it is considered desirable not to exceed 4 200 rad for ^{60}Co γ-rays in the cord when given in 20 fractions over 4 weeks

Side effects and early results will be reported in a later communication

Method

The patient is first positioned (Fig 1) under fluoroscopy to get the cervical and upper thoracic spinal cord as straight as possible It is an advantage if the cord is also horizontal, but usually this is not possible to achieve, and the straightened cord often forms an angle with the horizontal plane of the order 15 to 30 degrees The position of the patient is defined by cutting a silhouette cardboard to fit the patient (Fig 1)

The patient is then transferred to the mould room and positioned properly with the help of the silhouette cardboard A dorsal plastic cast (Fig 2) is produced, which extends from above the vertex to the level of the 7th thoracic vertebra

Patient contours perpendicular to the spinal cord are then obtained at representative levels In a patient with a nasopharyngeal tumour five different contours are drawn (Fig 3), viz at the levels of I nasopharynx, II tip of the mastoid, III submaxillary region, IV vocal cords, and V jugulum In a patient with a tumour of the hypopharynx, only contours III, IV and V are drawn A p and lateral films of known magnification are exposed, and the position of the tumour, target area, tissues of interest and reference points are indicated in the contours

The irradiation is administered (Fig. 4) through one ventral field (No 1) and 2 dorsal oblique wedged fields (Nos 2 and 3), all fields being oriented in a plane perpendicular to the cord If the nasopharynx is to be irradiated, lateral opposed fields with different [illegible] (fields 4 [illegible] of field [illegible] are treated with ^{60}Co at SSD 70 to 90 cm, whereas fields Nos 4 to 7 are treated with 8 MV roentgen radiation at SSD 100 cm The dose planning is performed individually for each patient Often the beam orientation of the posterior fields is 135 and 225 degrees from the direction of the ventral field, and they often receive 50 per cent of the peak absorbed dose of the ventral field In order to compensate for the relatively large absorbed dose in the midline from the dorsal fields or to diminish the absorbed dose in the spinal cord from the ventral field, different beam compensating filters are available for the ventral field The choice of filter depends among other things on whether there is tumour in the midline or not

The dose plan in three different sections for a patient with tumour of the hypopharynx appears in Fig 5 Tumour (marked in black) is only found in the neck region, section IV (Fig 5 b) The target area which besides the tumour includes the lymph

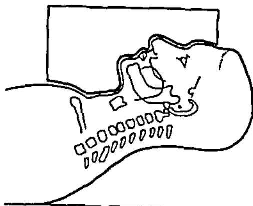


Fig 1

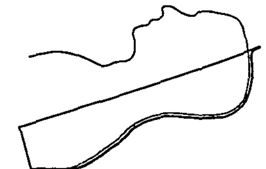


Fig 2

Fig 1 Positioning of the patient under fluoroscopy to obtain the spinal cord as straight as possible The position is defined by cutting a silhouette cardboard

Fig 2 Plastic cast used to immobilize the patient

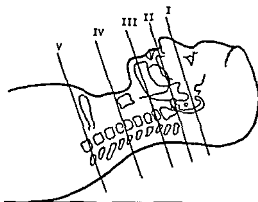


Fig 3

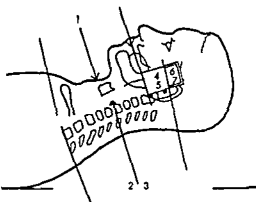


Fig 4

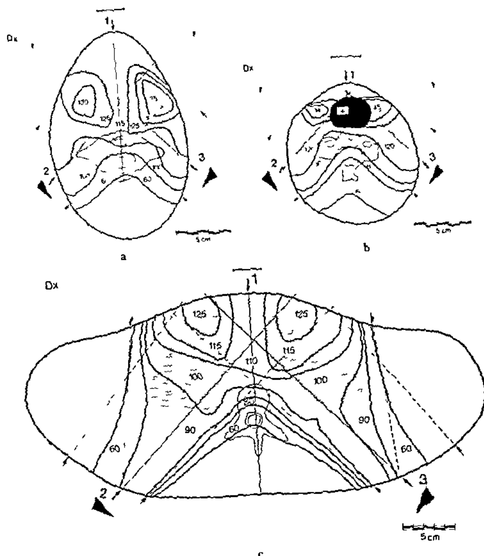
Fig 3 Cross sections for dose planning in a patient with carcinoma of the nasopharynx In a carcinoma of the hypopharynx where the nasopharynx is not to be treated only sections III IV and V are drawn

Fig 4 Field arrangement in a patient with carcinoma of the nasopharynx In a carcinoma of the hypopharynx where the nasopharynx is not be treated fields 2 and 3 share cranial border with field 1

nodes from the tip of the mastoid down to those in the supraclavicular fossa is indicated by the honeycombed area The vertebrae and the spinal cord are indicated from the films Further, the films demonstrate how the cross sections will be superimposed, an information necessary for the dose planning

The collimating system of the Gammatron I used for most of these irradiations is of the block type allowing for irregular fields (Fig 7 a) The center of the field does not necessarily have to coincide with the central beam (Fig 7 c) which may be advantageous when defining the SSD The field sizes are given by the number of opened lamellaelements and explains the decimal in the field sizes shown in the Figures

The dose planning is carried out with a computer (MÖLLER et coll 1976) The



SSD is put to the cross section in the neck region In the submaxillary and jugular cross sections (No III and V) *correction is done* to the real SSD which *is smaller in* these sections than *in the neck* section *Specially measured* isodose charts are used for the submaxillary and jugular sections taking into regard the somewhat smaller

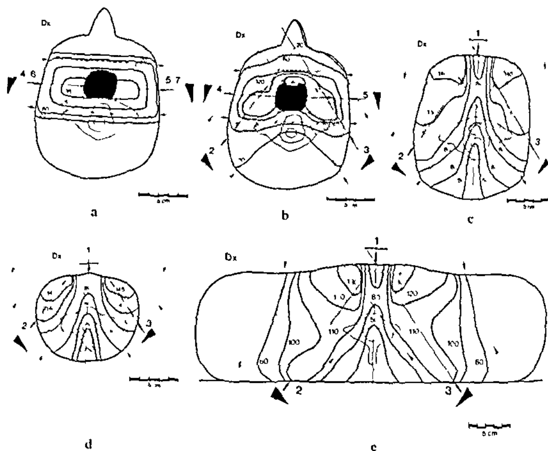


Fig 6 Carcinoma of the nasopharynx Dose plan for a) section I b) section II, c) section III, d) section IV an[illegible] 5 cm 6 cm 15 wedge filter Fields 6 [illegible] 00 cm SSD 50 % 5 cm 6 cm [illegible] 9 cm 45 wedge filter c) Field [illegible] 0 mm lead Fields 2 and 3 ^{60}Co [illegible] me as in c Fields 2 and 3 ^{60}Co [illegible] ne as in c Fields 2 and 3 same as in d

depth dose near the field edges in an elongated ^{60}Co field compared with the depth dose in the central ray Corrections are made for the vertebrae in the dose plans The peak absorbed dose of the ventral field is 100 per cent, and it is filtered in the treatment illustrated in Fig 5 with 4 mm Cu in the central part The dorsal oblique fields have 50 per cent peak absorbed dose and 45° wedge filters The broken lines indicate the geometrical edges of the fields In the dose plans the figures are written on the larger dose side of the isodose lines No contour compensating filters are used, and because of the higher per cent target dose in the neck region the fields have to be blocked in the neck region towards the end of treatment to level the absorbed dose in the whole target volume

The dose plans for a patient with tumour of the nasopharynx appear in Fig 6 For the sections through the submaxillary region, the neck and the jugulum (Fig 6 c, d, e) the technique is the same as previously demonstrated for a patient with



Fig 7 Carcinoma of the nasopharynx Portal films of a) field 1 b) fields 5 and 7 and c) field 3

carcinoma of the hypopharynx except for a 60 mm lead filter now being used in the ventral field instead of the copper filter The ventral field and the dorsal oblique fields end at different levels (Fig 4) and the caudal part of the nasopharynx is treated with the two dorsal oblique fields with 50 per cent peak absorbed dose and with two opposed wedged fields irradiated with 8 MV roentgen rays with 50 per cent field dose (Fig 6 b) Finally the most cranial part of the target that is the upper part of the nasopharynx and the base of the skull is treated with two opposed wedged fields with peak absorbed dose 50 per cent and two opposed fields without wedges and with peak absorbed dose 30 per cent (Fig 6 a) all fields irradiated with 8 MV roentgen rays It is an advantage if the fields join at different levels since this will reduce junction problems It must be realized that the nodes that are situated dorsally and cranially to the mastoid are only treated from the dorsal oblique fields and thus receive a small absorbed dose They are usually not included in the target but have been so in Fig 6 b in order to emphasize this point The peak absorbed doses 50

a

b



c

Fig 8 a) Treatment set up for field I in a patient with metastatic disease from a previously irradiated carcinoma of the lower lip Patient supine lying in the cast Beam compensating filter of lead (black arrow) Shield for the lower lip (white arrow) b) Set up for field 3 All fields are irradiated with the patient in the same position c) Set up for field 2 The central beam is perpendicular to the cord

and 30 per cent for the fields irradiated with 8 MV roentgen rays have been chosen to give the same target absorbed dose in the base of the skull, nasopharynx, and submaxillary region Also in this type of treatment the neck has to be shielded towards the end of the treatment course

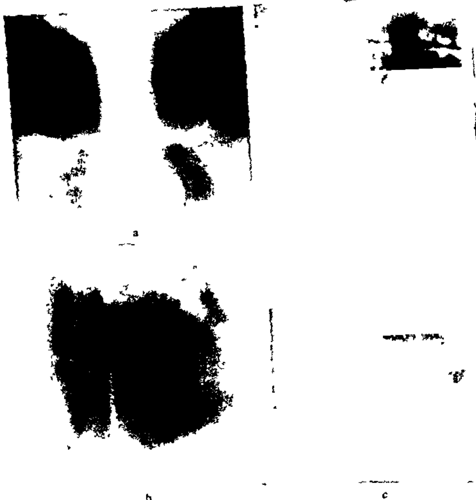


Fig 9 Carcinoma of the nasopharynx. a) Film of field 1 The beam compensating filter of lead is clearly visible b) Fields 5 and 7 c) Field 3

The beam entrances and geometrical edges of the fields are localized on the patient under fluoroscopy and drawn on the patient and on the cast Films of the ports are obtained and corrections, if indicated, are performed Representative portal films for a patient with carcinoma of the nasopharynx are demonstrated in Fig 7

The treatment set up for the ventral field appears in Fig 8 a The central beam is directed perpendicular to the spinal cord, and the field therefore has to be tilted, in this case about 15 degrees The beam compensating filter is seen just under the collimator there was no target in the midline and therefore a thick compensating filter was used Because of previous irradiation towards this region, a shield for the



Fig 10 Carcinoma of the hypopharynx Film of field 1 The beam compensating filter of copper is not recognizable

lower lip was used It consisted of a 5 cm thick lead block, cut to suit the beam geometry, and placed on a perspex plate about 20 cm above the patient

The treatment set up for one of the posterior oblique fields (No 3) appears in Fig 8 b, c The position of the patient is the same for all fields Windows have been cut in the cast to retain the skin sparing effect of the ^{60}Co γ-rays

The ^{60}Co unit used has been either a Siemens Gammatron I (Fig 8) or a Siemens Gammatron III

Slow films (Figs 9, 10) are exposed at the first fraction Repositioning of the fields may then prove necessary, and films are exposed until it is felt that the positioning of the ports is correctly reproduced

For each field the peak absorbed dose is determined at the first fraction with a cable connected ionization chamber The absorbed dose at the eyes is determined either with small ionization chambers or with TLD frequently during the whole course of treatment to control the dose to the eyes, which may be critical due to maladjustment of the posterior fields

As soon as the films agree with the dose plan and the treatment set up, the absorbed dose in the nasopharynx, mouth, pharynx and hypopharynx is determined using small ionization chambers placed in plastic catheters together with indicators and then inserted Each measurement is repeated at least once Examples of films obtained during fractions when such measurements were carried out appear in Figs 11 and 12 The position of the different measuring points is defined by the indicators The measured values for absorbed dose as well as the calculated values according to the dose plans are also indicated If there is a difference between the measured and

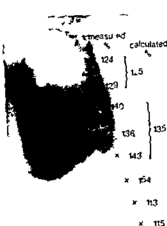


Fig 11

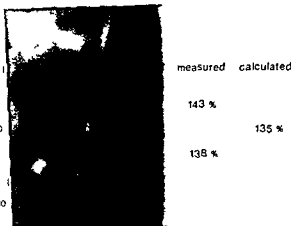


Fig 12

Fig 11 Film of field 3 Position of plastic catheters with 8 ionization chambers and lead indicators in the hypopharynx Measured values for absorbed dose to the left and calculated values according to the dose plan to the right

Fig 12 Film of fields 5 and 7 Position of plastic catheters with two ionization chambers and lead indicators in the nasopharynx Measured values for absorbed dose to the left and calculated values according to the dose plan to the right

calculated absorbed doses in excess of 6 to 8 per cent, the reason must be sought for (MÖLLER et coll)

All fields are irradiated daily 5 days a week A mean target absorbed dose of 200 rad per fraction is aimed at Usually split course treatment is used with two thirds of the total absorbed dose in the first series and an interval of 4 weeks between the two series

Results

The treatment charts for 68 consecutively treated patients were reviewed (Tables 1 2) The minimum absorbed dose in the tumour was taken as the representative dose (100 per cent) The maximum and the minimum target absorbed doses were

Table 1

Variation in total absorbed dose in the target and in the spinal cord in relation to the representative dose (in per cent)

	Maximum target dose	Representative dose = minimum absorbed dose in tumour	Minimum target dose	Absorbed dose in the spinal cord
Range	145 105	100	100–70	90–50
Mean	115		85	70
S D	7		6	9

Table 2

Total representative dose (= minimum absorbed dose in tumour) and absorbed dose in the spinal cord in 68 patients

	Representative dose	Absorbed dose in the spinal cord
Range	6 500–4 200 rad	5 600–2 400 rad
Mean	5 800	4 000
S D	575	550

usually within ±15 per cent of the representative dose In the 68 patients the target absorbed dose had been mean 5 800 rad ±15 per cent, and the absorbed dose in the spinal cord mean 4 000 rad

When starting a new technique of such a complex nature as the one described, certain problems of technical nature are to be expected Such were also encountered in the first patients treated, but proved to be possible to overcome It is very important that the positioning of the patient is well defined and reproduceable at each fraction Also the anatomic planning should be very carefully performed The technique has now proved to be feasible for clinical routine, and it is at present the standard method for treating tumours of the head and neck and their lymphatics In order to achieve optimum results, repeat control measures and a close surveillance of the irradiation by the therapist and the physicist in close cooperation is necessary

SUMMARY

A technique for en bloc irradiation of tumours of the head and neck and their lymphatics, as well as its dosimetry and control measures, are reported

ZUSAMMENFASSUNG

Eine Technik zur En bloc-Bestrahlung von Kopf und Nacken-Tumoren und deren Lymphknoten sowie die zugehorige Dosimetrie und die Kontrollmessungen werden beschrieben

RESUME

Présentation d une technique pour l irradiation en bloc de la tete et des tumeurs du cou et de leurs lymphatiques et présentation de la dosimétrie et des mesures de controle de cette technique

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EFFECT OF LUNG IRRADIATION ON THE INCIDENCE OF PULMONARY METASTASES AND ITS MECHANISM

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Prevention of the spread and growth of metastases is a very important objective in the treatment of malignant tumours The relation of radiation and anticancer drugs to tumour metastases is not yet clearly understood despite its importance Well-defined experimental models are an essential for improved understanding In the present work, in which mice were injected with the LP-12 sub-line of Ehrlich ascites cells (HASEGAWA et coll 1970) via the tail vein, colonies formed in the lungs were counted to estimate the relationship between the number of cells injected and the pulmonary colony count

It has been reported that irradiation of the lungs before injection of tumour cells enhanced pulmonary metastases (BROWN & PHIL 1973, DAO & YOGO 1967, FIDLER & ZEIDMAN 1972, FISHER & FISHER 1969, MILAS & WITHERS 1970) This is of great clinical importance in relation to prophylactic lung irradiation but the underlying mechanism has not been fully investigated (BROWN & PHIL) The present investigation was undertaken to analyse the role of irradiation, at various time intervals before the injection of tumour cells, in increasing pulmonary metastases It was also sought to elucidate the mechanism of enhancement, mainly with reference to changes in pulmonary blood vessels, particularly vascular permeability, which may be brought about by irradiation

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Material and Methods

A sub-line from the original Ehrlich carcinoma cells was used (LP-12, lung-passaged sub-line of Ehrlich carcinoma), which prefers to grow in the lung and with 100 per cent of lethal take in hosts within a relatively short period The modal number of chromosomes in the original and the LP-12 cell line was found to be 72 (27 per cent) and 73 (43 per cent), respectively (HASEGAWA et coll)

Male ddY mice, weighing 20 to 30 g, were used and given water freely The LP-12 sub-line of Ehrlich ascites carcinoma cells, which were maintained by serial intraperitoneal transplantation into ddY male mice, were employed for the experiments Tumour cells harvested 7 days after transplantation were used and a hemocytometer count was made of cells, excluding erythrocytes, which did not stain with Erythrosin A (0 5 per cent) Dilutions were then prepared as required and 0 2 ml was injected into the tail vein of each mouse Ten to 12 days after injection the mice were killed, and their lungs removed and fixed in Bouin's fluid The lobes of the lung were separated and the total number of visible colonies per lung was recorded

Irradiation was carried out on the right lung field alone, using β-rays from a *Betatron* (18 MeV, Siemens) at a dose rate of 200 rad/min, with the contralateral lung field, protected by a lead plate, serving as the control

The procedure for determination of vascular permeability (the extravasation rate of plasma protein) was almost the same as that described by SONG & LEVITT (1971) Whole blood (0 5 ml) taken from a normal mouse, was incubated with 30 μCi of sodium ^{51}Cr-chromate for 60 min in a water bath of 37°C and unbound ^{51}Cr was removed by washing several times with isotonic saline The labeled red blood cells were then mixed with 20 to 30 μCi of ^{125}I-labeled human serum albumin and the volume adjusted to the original 2 ml with saline About 0 1 ml of this mixture was injected through the tail vein One hour after injection, 1 ml of blood was withdrawn by cardiac puncture The activity of ^{51}Cr and ^{125}I in the tumours, blood, and plasma was counted with a γ scintillation spectrometer and vascular permeability in each tumour was calculated according to the following formula

Vascular volume

$$\text{ml of blood/tumour} = \frac{^{51}\text{Cr activity/tumour}}{^{51}\text{Cr activity/ml of blood}}$$

Vascular permeability

ml of plasma extravasate in 1 h/ tumour = total plasma in tumour—intravascular plasma in tumour

$$\text{Where total plasma} = \frac{^{125}\text{I activity/tumour}}{^{125}\text{I activity/ml of plasma}}$$

$$\text{and intravascular plasma} = \text{vascular volume} \times \left(1 - \frac{\text{hematocrit}}{100}\right)$$

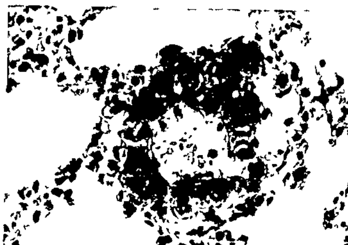


Fig 1 Microscopy of the pulmonary metastases 2 days after intravenous injection of the tumour cells, which surround a capillary vessel like a rosette (× 450)



Fig 2 Bilateral pulmonary metastases in a male mouse following the intravenous injection of tumour cell suspension (4.4×10^6 cells)



Fig 3 Microscopy of the pulmonary metastases 11 days after the intravenous injection Innumerable nodules in the lung tissue (× 40)

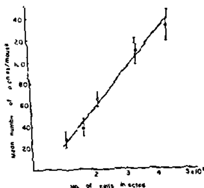


Fig 4

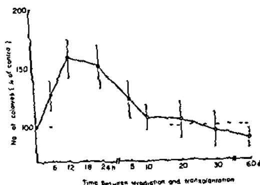


Fig 5

Fig 4 The mean number of colonies mouse in both lungs observed after different numbers of non-stained unirradiated cells have been injected

Fig. 5 The number of lung colonies (% of control) of intravenously injected LP 12 cells as a function of the time between irradiation of the lungs with 2 000 rad and the injection of the cells The dotted line is the average value of control lungs Closed symbols significant difference ($P < 0.05$) open symbols insignificant difference (n 6–12)

Result

Pulmonary colony formation and its microscopic features Microscopy of pulmonary tissues from mice killed 2 days after intravenous injection of tumour cells revealed the presence of rosettes of tumour cells in the pericapillary region (Fig 1) The tumour foci continued to grow, becoming grossly demonstrable colonies of 1 to 2 mm in diameter about 10 days after transplantation (Figs 2, 3) Since these colonies were distributed uniformly not only in the lungs but over the pulmonary surfaces as well (Fig 3) it was practicable to estimate the total number of colonies present from the superficial colony count

Interrelation between the number of injected cells and the pulmonary colony count (Fig 4) A linear relationship existed between the number of tumour cells injected and the pulmonary colony count (i e, total number of superficial colonies of both lungs) This was demonstrable within the range of injected cell numbers between 1×10^6 and 4×10^6, whereas, beyond this range the colonies formed tended to be confluent and could scarcely be counted Below this range, on the other hand, errors were frequently made in the estimation of total colony counts Therefore, the experiments were carried out with the number of intravenously injected tumour cells adjusted to lie within the range of linear relationship

Influence of pulmonary irradiation on metastases to the lungs Mice were irradiated in a dose of 2 000 rad over the right lung field, followed by injection of LP-12 cells

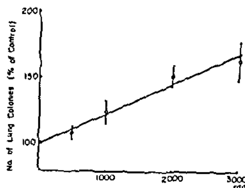


Fig 6

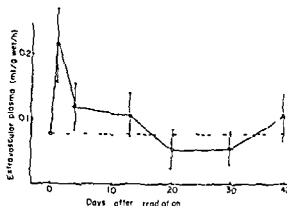


Fig 7

Fig 6 The number of lung colonies (% of control) of intravenously injected LP-12 cells as a function of the lung dose delivered 24 hours before cell injection

Fig 7 Changes in extravasation rate of plasma following irradiation with 2 000 rad in a single exposure The dotted line represents an average value of control lungs Closed symbols significant difference ($P < 0.05$), open symbols insignificant difference ($n = 7$–12)

at various time intervals, and pulmonary colony counts made The pulmonary colony counts in the right lung were found to increase progressively over those in the non-irradiated left lung (control) with an increasing interval between irradiation and tumour transplantation, with a maximal increase at 12 hours (Fig 5) Subsequently, the increase declined gradually and reversed slightly in mice receiving tumour cell transplantation between 30 and 60 days after irradiation

Fig 6 illustrates the interrelation between dosage and colony count of the irradiated lung in animals given tumour cell injection 24 hours after unilateral exposure to radiation A linear relationship was observed with dosages ranging from 1 000 to 3 000 rad

Effect of irradiation on pulmonary vascular permeability The amount of extravascular plasma in the lungs was determined at various time intervals after irradiation with a dose of 2 000 rad Extravasation of blood plasma in the irradiated lung steadily increased reaching a peak at 12 hours, with a subsequent gradual decline (Fig 7) It is evident that the curve is quite comparable to that in Fig 5

Discussion

It has been demonstrated in the experiments that irradiation before inoculation enhances pulmonary metastases of intravenously injected tumour cells This finding is in good agreement with the results of experiments in rats reported by Dao & Yogo This enhancement is significant as early as a few hours after irradiation and subsides to the pre-irradiation level after several weeks in the present experiments This phenomenon has been thought to be transitory in nature and related to the dose or irradiation The underlying mechanism has not been clearly elucidated, as yet

Increased metastases of tumour transplanted to the lungs by whole body irradiation as well as by irradiation of the lungs alone was reported by BROWN & PHIL, DAO & YOGO FISHER & FISHER, MILAS & WITHERS The present experiments also reveal the same findings in mice, with unilateral protection of one lung against irradiation These results suggest that immunologic phenomena were not responsible for the enhanced number of colonies in the irradiated lungs

It is conceivable that the enhancement of metastases to irradiated lungs is due to inactivation of macrophage phagocytosis by irradiation Experiments with ^{125}IUDR labeled tumour cells have shown however, a significant difference in the number of the cells retained between the normal and irradiated lung (BROWN & PHIL) It is difficult to explain increased metastases by irradiation with this hypothesis insomuch as phagocytosis by macrophages is known to be radiation resistant and furthermore that this takes place a few hours after irradiation

The hypothesis which seems to provide the most convincing explanation of this phenomenon is that irradiation directly affects the capillary endothelial cells causing inflammatory changes, vascular dilatation, increased permeability, etc, which, in turn, cause diminution in blood flow rate and marked changes of the blood capillaries resulting in reduction in the rate of clearance of tumour cells from the lungs (BROWN & PHIL, JOLLES & HARRISON 1966) It seems probable that irradiation might increase the rate at which the trapped tumour cells can migrate through the endothelium into the perivascular connective tissue

In the present experiments with ^{125}I human serum albumin and ^{51}Cr labeled erythrocytes the pulmonary blood vessels were found to have post irradiation permeability changes analogous to that of pulmonary metastases of injected tumour cells This seems to confirm the fact that increased vascular permeability contributes to the establishment of metastases (FIDLER & ZEIDMAN)

These results are applicable to radiation therapy of malignant tumours, it would be advisable not to give unnecessary irradiation to the lungs without due consideration and anticoagulants may be administered They also indicate that the lung colony assay not only facilitates understanding of the mechanism of metastases and the effect of irradiation on tumour metastases (SHAEFFER et coll 1973, WEXLER 1966), but also serves as a useful means of assessing sensitivity of a tumour irradiated in vivo (HILL & BUSH 1969) as well as the effectiveness of anticancer drugs

SUMMARY

LP 12 cells injected intravenously into ddY mice result in the formation of visible lung colonies which are introduced as a model for pulmonary metastases Localized irradiation before tumour cell transplantation significantly increased the incidence of pulmonary metastases in the irradiated lung only The changes of the vascular permeability of the lung indicate that dilatation of capillaries or increased permeability may be one of the main mechanisms of this phenomenon

quency of T-lymphocytes decreases to a higher extent than non-T-lymphocytes—mainly B-lymphocytes—(STJARNSWARD et coll) whereas others have obtained the reverse results (BLOMGREN et coll 1974 b, c) (For a review of T-and B lymphocytes, see GREAVES et coll 1974)

In the present report the responses of human peripheral lymphocytes to various specific and unspecific mitogens following irradiation in vitro are analysed

Materials and Methods

Eight members of the staff, 20 to 60 years old, served as lymphocyte donors Venous blood was drawn in heparinized syringes and the nucleated cells separated by Ficoll-Isopaque gradient centrifugation as previously described (JONDAL et coll 1972) The cells were then washed twice by centrifugation in Eagle's Minimal Essential Medium supplemented with Earle's salts (MEM) Such cell suspensions, regularly containing 90 to 95 per cent of lymphoid cells, will hereafter be termed non-purified In some experiments such preparations were depleted of phagocytic cells This was performed by adding carbonyl iron powder to the suspensions These particles, and hence also cells which ingested iron, were then removed by a magnet by the method of BLOMGREN (1974) The resulting suspensions, will hereafter be designated Fe-purified

These preparations of highly purified lymphocytes were used for the preparation of cell suspensions enriched for T- and B cells Separation of T- and B cells was performed using the method described by JONDAL (1974) In short, lymphocytes were incubated with sheep erythrocytes (SRBC) During this step SRBC will adhere to T-cells in an immunologically nonspecific way (BRAIN et coll 1970, BRAIN & GORDON 1971) The cell suspensions were then suspended in fetal calf serum and centrifuged on a Ficoll-Isopaque gradient Due to the higher density, the T-cell-SRBC-complexes will sediment whereas non-SRBC adhering cells, mainly B cells, will stay at the fluid interface For simplicity the precipitating cells will hereafter be termed T-cells and the cells at the fluid interface B cells The T-cells were exposed to a solution of ammonium chloride to lyse SRBC before used for experiments Using the capacity of T-cells to adhere SRBC as a marker (BLOMGREN 1974), it was found that non-purified and Fe purified cell preparations contained 60 to 65 per cent of T cells and the T and B cell preparations 90 to 95 and 10 to 15 per cent, respectively The number of cells was determined in a Burker chamber after crystal violet staining

Various cell preparations, suspended in MEM at a concentration of 1 0 × 10^6 cells/ml, were poured into glass Petri dishes (6 cm × 6 cm) forming a fluid depth of 2 to 3 mm They were then exposed to various doses using a Siemens machine The physical factors were 140 kV, 20 mA, 4 Al-added filter, HVL 0 45 mm Cu, focus target distance 40 cm The irradiations were performed at room temperature The exposure rate, in the centre of the 16 cm × 16 cm beam used for simultaneous

irradiation of 4 Petri dishes, was determined by ionisation chamber measurements The homogeneity of the beam was checked by photographic dosimetry The average exposure rate in the suspension was determined to 113 R/min ± 10 per cent

The well known inhomogeneity in the absorbed dose at the interface between the glass and the suspensions has been neglected since it concerns only a very thin layer (< 50 μm) and the results are based on intercomparisons of suspensions irradiated under equal conditions

Unless otherwise stated, each well contained $1\,0 \times 10^5$ cells suspended in 0 2 ml of MEM supplemented with 10 per cent of heat inactivated human serum, penicillin and streptomycin Half of the cultures received a stimulant and the others served as controls The stimulants were (1) phytohaemagglutinin (PHA, Bacto-Phytohaemagglutinin M, Difco lab, Detroit, Mich, USA), (2) poke weed mitogen (PWM, Grand Island Biological Co, N Y, USA) The contents of commercially available vials of PHA and PWM were dissolved in 5 0 ml of MEM These solutions will hereafter be termed 100 % of PHA and PWM, respectively (3) Concanavalin A (ConA, Sigma Chemical Co, St Louis, Mo, USA) was dissolved in MEM The final concentration of ConA in the cultures is expressed as μg) ml (4) Purified protein derivate of tuberculin (PPD tuberculin, RT 22, Statens Seruminstitut, Copenhagen, Denmark) (5) Allogeneic or syngeneic non purified lymphocytes previously treated with mitomycin C as described previously (BLOMGREN et coll 1974 a) Cultures receiving allogeneic cells, mixed lymphocyte cultures (MLC) contained $2\,0 \times 10^5$ responding cells and the same number of stimulating cells

After 4 days of incubation at 37°C in a humidified 5 % CO_2 air atmosphere, each culture received 1 μCi of ^3H thymidine (The radiochemical Center, Amersham, England Specific activity 5 mCi/mM) Twentyfour hours later the cultures were terminated by being placed at −20 C When convenient, the cultures were thawed and the fluid of each well passed through a microfilter which retains particulate material This procedure was performed with the aid of a semiautomatic multiple-sample processor (Skatron, Box 3401, Lierbyen, Norway)

The filters were then placed in vials containing scintillation fluid and the activity measured by a liquid scintillation counter The culture conditions and measurements of activity have been described in detail by LILLIEHÖÖK & BLOMGREN (1974)

The activity was expressed as counts per minutes (cpm) Isotope uptakes of unstimulated control cultures were subtracted from those obtained in corresponding stimulated cultures The activity of cultures containing irradiated cells was related to the values obtained in corresponding non irradiated cultures The mean values of triplicate cultures were calculated on an arithmetic basis and expressed as per cent stimulation

Results

Responsiveness of irradiated lymphocytes to phytomitogens Preparations of non purified lymphocytes were exposed to various doses of irradiation They were then

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Table 1

Absolute stimulations, expressed as CPM, of non irradiated non-purified preparations of lymphocytes exposed to 3 per cent of PHA and their proportions of cells resistant to radiation The relative stimulations after exposure to various radiation doses are illustrated in Fig 1

Experiment*	³H thymidine incorporations (mean CPM)	Fraction of resistant cells** (per cent)	Radiation dose (R)
A	288 397	33 2	800–3 200
B	114 820	31 1	800–3 200
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D	42 650	34 8	800–3 200

* The experiments refer to those presented in the diagrams of Fig 1

** The linear regression equations, $y = kx + 1$ of the relative PHA stimulations of cell preparations exposed to doses indicated within parenthesis were calculated (Fig 1) The resistant fraction was determined by extrapolation to 0 R

stimulations of the non-irradiated cultures and the size of the resistant cell populations are listed in Table 2

Responsiveness of irradiated lymphocytes to antigens The sensitivity of the responding cells of non-purified cell preparations involved in the MLC-reaction was also investigated Fig 3 presents the results of three such experiments using different donors of both responding and stimulating cells The ³H-thymidine uptake was markedly reduced by exposing the cells with doses up to 400 or 800 R

Higher doses caused little or no further decrease of isotope incorporations The stimulation of the non irradiated allogeneic mixtures and the proportions of resistant MLC-reactive lymphocytes are listed in Table 3

The responsiveness of irradiated non purified lymphocytes to PPD was also tested after irradiation Fig 4 illustrates the results of two such experiments The responsiveness of the cells to this antigen decreased in a fairly linear fashion with increasing doses There was no tendency of the curves to plateau off at higher doses In all tests the specific stimulation of cells exposed to 3 200 R was less than 1 per cent of that obtained in non-irradiated cultures The absolute stimulations of non-irradiated PPD-exposed cultures are presented in Table 4

Responsiveness of irradiated fractionated T- and B-lymphocytes to PHA The results presented may indicate that polyclonal mitogens and allogeneic cells *stimulate* two populations of lymphocytes which differ with regard to sensitivity Methods to separate

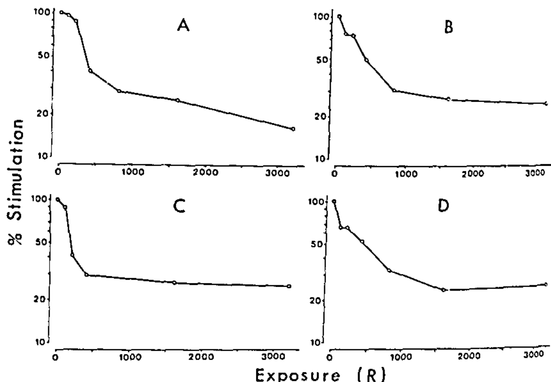


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exposed to 3 % of PHA 1 to 1½ hours after irradiation and their proliferative responses to this agent determined at day 4 Fig 1 illustrates that there was a sharp reduction of ³H-thymidine uptakes of the cultures by increasing the dose from 100 to 400 or 800 R A further increase of irradiation dose only marginally decreased the PHA-response, thus creating a two dose shaped curve The results indicate that there are two populations of PHA-responsive lymphocytes, one which is relatively sensitive and one which is relatively resistant

By determining the linear regression equation, $y = kx + 1$, for the values obtained in cell cultures yielding the plateaus of the curves, the proportion of 'resistant' PHA-responsive lymphocytes in the unirradiated cell preparations may be calculated Table 1 shows the actual stimulations, expressed as cpm, of the non-irradiated mitogen stimulated cultures and the calculated proportions of the 'resistant' cell populations of the experiments are illustrated in Fig 1

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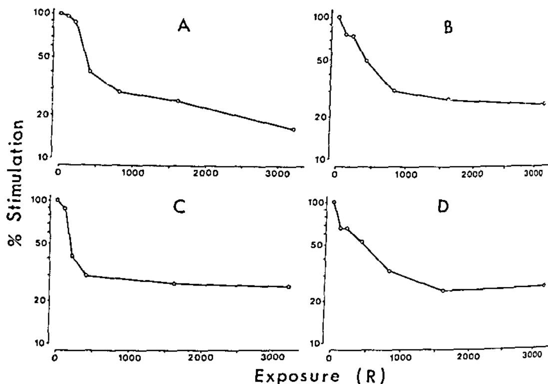


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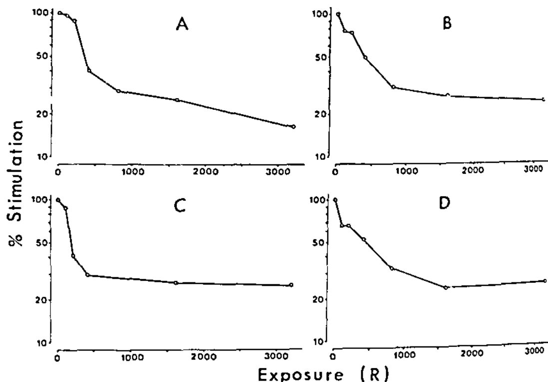


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Table 4

Absolute stimulations of non irradiated cells exposed to PPD The relative stimulations of irradiated cells are presented in Fig 4

Experiment	PPD-concentration (µg/ml)	³H thymidine incorporations (mean CPM)
A	100	4 519
	10	9 772
B	100	14 790
	10	21 800
	1 0	22 910
	0 1	19 055

Table 5

Absolute stimulations of non-irradiated cells and proportions of resistant cells of the various cell preparations exposed to 3 per cent of PHA presented in Fig 5

Experiment	Cell preparation	³H thymidine incorporations (mean CPM)	Fraction of resistant cells (per cent)	Radiation dose (R)
A	Non purified	101 950	18 1	800–3 200
	Fe purified	85 110	17 9	800–3 200
	T-cells	83 445	21 3	800–3 200
	B-cells	13 975	—	
B	Non purified	124 800	14 4	800–3 200
	Fe purified	154 800	9 1	800–3 200
	T-cells	101 700	17 8	800–3 200
	B-cells	14 125	—	

In the present tests, a mitogenic stimulus was added 1 to 1½ hours after *irradiation* of the cells Under these experimental conditions it was calculated that the resistant phytomitogen responsive sub-population of cells made up 10 to 40 per cent of the whole cell population Other authors have presented data showing that the sensitivity of the cells may vary depending on when they are exposed to the mitogen They become more sensitive as the *time interval* between exposure and addition of mitogen is increased (SCHREK & STEFANI 1964, VAUGHAN SMITH & LING 1974) One explanation for this phenomenon is that phytomitogens

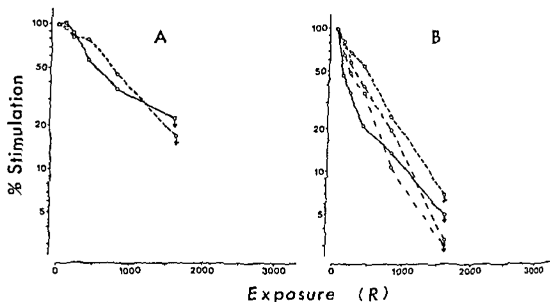


Fig 4 Relative ^{3}H-thymidine uptakes of irradiated non-purified lymphocyte preparations exposed to various concentrations of PPD Two different lymphocyte donors, selected for strong in vitro PPD-responses, were employed 100 μg/ml O—O, 10 μg/ml O---O, 1 0 μg/ml O- -O, 0 1 μg/ml O- -O Arrows indicate that the stimulations of cells exposed to 3 200 R were less then 0 5 %

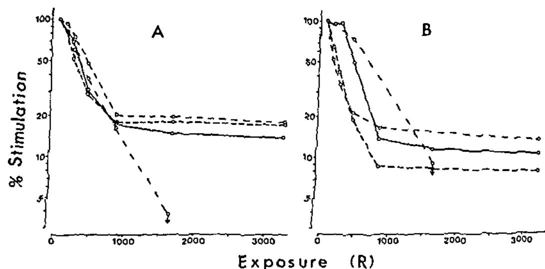


Fig 5 Relative ^{3}H-thymidine uptakes of
of PHA The diagram present the results
Non purified O—O, Fe purified O --O,
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parts of the organ and those which are more resistant in the thymic medulla (TROWELL 1961) These two cell populations also differ with regard to sensitivity to the lytic effect of adrenal corticosteroids (ISHIDATE & METCALF 1963) and immunologic competence (BLOMGREN & ANDERSSON 1968, 1971)

assistance Mr Ingmar Lax has been helpful with dosimetric problems which is gratefully acknowledged This investigation was supported by grants from Swedish Cancer Society, the Hasselgrens Fond and the Lotten Bohman Fond

SUMMARY

Human lymphocytes were exposed to varying doses of roentgen irradiation in vitro and thereafter tested for reactivity to different polyclonal mitogens and antigens using DNA synthesis as a marker for viability The dose response profiles obtained indicate that there are two subpopulations of lymphocytes which are responsive to phytohaemagglutinin, poke weed mitogen, concanavalin A and allogeneic cells One is relatively sensitive to radiation and the other is relatively resistant However, no 'resistant' PPD tuberculin responsive cell population could be detected Irradiated lymphocyte populations enriched for T-cells exhibited both a sensitive and a resistant PHA-responsive population, whereas cell populations enriched for B-cells only exhibited a radiation sensitive one

ZUSAMMENFASSUNG

Menschliche Lymphozyten wurden in vitro unterschiedlichen Dosen von Rontgenstrahlen ausgesetzt und danach deren Reaktivität gegenuber verschiedenen polyclonalen Mitogenen und Antigenen unter Verwendung der DNS-Synthese als Kennzeichen fur deren Viabilität [illegible]

eine resistente PHA-empfindliche Population, während Zellpopulationen, in denen nur B-Lymphozyten angereichert worden waren, nur eine Strahlen-empfindliche Population zeigten

RÉSUMÉ

Des lymphocytes humains ont eté exposés à differentes doses de rayons de Roentgen in [illegible]

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[illegible]

responsive lymphocyte population is homogeneous with respect to sensitivity However, the cell population may be heterogenous with regard to responsiveness to a phytomitogen Those which are triggered to protein synthesis very soon after the mitogen has combined with its membranes associated receptor will survive Lymphocytes which are activated late after the 'mitogen signal' will die because of a deficient repair system The highly mitogen responsive lymphocytes could thus represent the resistant cell population Another explanation could be that lymphocytes with a short generation time die after a short time period, whereas cells with a longer generation time survive for a longer time after irradiation

There is evidence that phytomitogen lectins induce blast transformation of mainly T-cells in the human (JONDAL 1974)

However, several authors have found that B-cells are also blast transformed in such cultures (PHILLIPS & ROITT 1973, PHILLIPS & WEISROSE 1974, MELLSTEDT et coll 1973) It is possible that human B-cells are unresponsive to phytomitogens but become transformed by soluble mediators released by phytomitogen activated T-cells Such an observation has been made using Tetanus toxoid (GEHA & MERLER 1974) or PPD (BLOMGREN 1975) as a stimulatory agent In the present investigation the PHA-responses of irradiated cell population enriched for T- and non-T-cells (mainly B-cells) were examined It was observed that the dose response profiles of T-cells was similar to that of the original non-purified cell population However, the B cell preparations differed in the sense that there was no sign of the presence of any resistant cell population One interpretation of these results is that non-T-lymphocytes are normally activated late after the addition of PHA Thus, they will die in a dormant stage after irradiation, before having had time to build up any repair system

Interestingly, the PPD-responsive lymphocyte population did not exhibit any detectable subpopulation of resistant cells Evidently, this is not a specific trait of antigen reactive cell populations, since a resistant subpopulation could be sharply distinguished amongst MLC-responsive lymphocytes It may be of relevance that the majority of the PPD-responsive lymphocytes have been presensitized to this antigen and the response in vitro may be regarded as a booster stimulation This is not the case with lymphocytes which are responsive in the MLC

In conclusion, by comparing the results of the present investigation with in vitro irradiation, with those of lymphocyte reactivity of patients having received external radiation therapy, certain points of agreement may be observed (1) the phytomitogen responses of lymphocytes is not abolished even after massive doses of ionizing radiation, (2) tuberculin reactivity of lymphocytes disappears by relatively small doses of radiation

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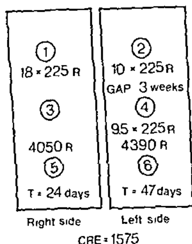


Fig 1 Treatment schedule for bilateral treatment of the parasternal region with 200 kV roentgen rays (HVL 1 2 mm Cu) On the marked regions (1 to 6) reflectance spectrophotometer measurements were performed

fore a gap of G days (ELLIS 1969, WINSTON et coll 1969) Recently KIRK et coll (1974) have presented a gap correction to the CRE-system This correction is $e^{-0.008G}$, where G is the number of days the gap lasts The two corrections will be discussed later on

In the present analysis ELLIS' gap correction in the CRE-formula is used If the subtolerance level after the first part of the treatment of T days before a gap of G days is expressed as CRE (I), and the reduced effect after the gap is called CRE (II), then

$$\text{CRE (II)} = \text{CRE (I)} \left(\frac{T}{T+G}\right)^{0.11}$$

Thus CRE (II) describes the radiation effect just before starting the second part of the treatment

The biologic effect of different prospectively calculated dose schedules was controlled by the same technique of reflectance spectrophotometer measurements as previously (TURESSON & NOTTER)

If skin reaction as a biologic parameter for the radiation effect is used to evaluate the reliability of the CRE function, the radiation sensitivity of the skin and the accuracy of the spectrophotometer measurements must be known Therefore in the present series the minimum dose difference causing a measurable difference in erythema and pigmentation has been investigated

Material and Methods

To investigate the gap-correction 14 patients with mammary carcinoma (of whom 4 were operated upon the left and 10 on the right side) were irradiated postoperatively on bilateral parasternal fields of 5 cm × 12 cm with 200 kV roentgen rays

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SKIN REACTION AS A BIOLOGIC PARAMETER FOR CONTROL OF DIFFERENT DOSE SCHEDULES AND GAP CORRECTION

INGELA TURESSON and G NOTTER

Biologic effects on normal tissue for fractionated irradiations can be calculated by the Cumulative Radiation Effect (CRE)-formula (KIRK et coll 1971)

$$CRE \quad \left(\frac{T}{N}\right)^{0\ 11} d \ N^{0\ 65}$$

The formula describes the biologic effect on normal tissue for fractionated irradiation when T is the treatment time in days, N the number of fractions and d the dose per fraction in rad defined for ^{60}Co radiation The formula has previously been used for prospective dose calculations of daily and 'twice a week' irradiation on bilateral parasternal fields in patients operated upon for carcinoma of the breast (TURESSON & NOTTER 1975) The result showed that the CRE formula was useful for prospective calculation of biologically equivalent radiation doses with different fractionation

With the increasing use of varying gaps during irradiation courses it is essential to modify the total dose with reference to the recovery and especially the repopulation of the normal tissues ELLIS has, for calculation of gaps in the NSD-formula, proposed the correction $(T/T+G)^{0\ 11}$, where T is the number of treatment days be-

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Table 1

Mean values and total means (in per cent) of exposure measured with TLD for the 14 patients in the gap series' according to measurement points 1 to 6 and corresponding CRE (95 per cent confidence)

Patient No	Measurement point					
	1	2	3	4	5	6
1	94 8±1 7	95 7±2 4	94 8±1 7	96 1±1 7	92.1±1 8	93 1±2 1
2	94 5±2.6	93 8±3 1	92 7±2 0	93 8±1 9	87 9±1 6	92 5±1 8
3	93 4±2 6	96 2±3 3	96 9±1 9	95 8±2 7	92 8±1 6	92 8±3 1
4	91 3±1 9	92.9±2 8	92 1±1 9	93 3±2 8	90 1±1 5	88 3±2 1
5	92 1±1 8	92 5±2 7	92 7±1 5	93 6±2 1	89 6±1 6	89 8±1 9
6	95 8±2.7	93 9±3 1	95 6±2 5	94 8±2 7	93 0±3 1	90 3±2.1
7	92 4±4 3	93 3±3 7	92 3±2 4	91 8±3 8	88 9±3 7	89 6±4 5
8	93 7±3 1	90 7±3 0	94 3±2.3	91 6±3 0	90 3±2 0	89 9±3 0
9	96 5±4 0	94 7±2 7	95 1±2 9	95 5±3 1	94 7±3 4	94 2±2.6
10	96 0±2.9	96 3±2 5	98 5±3 4	96 1±2 8	95 4±2 3	97 4±2.9
11	98 0±2.6	98 4±2 9	96 2±2 2	98 6±2 5	92 6±2.3	95 7±2 3
12	96 5±2 4	97 5±2 2	96 8±2 3	97 6±2 3	95 5±2 8	95 8±2 2
13	98 8±1 6	98 9±2 3	99 8±1 9	101 3±2 6	96 6±2 0	96 9±2.9
14	105 4±2.1	103 6±2 3	104 7±2 4	104 8±2 1	103 9±2 5	103 6±2 4
Total mean	95 7+2 1	95 6±1 9	95 9±2 0	96 1±2 1	93 1±2 4	93 5±2.4
CRE	1 548±20	1 549±24	1 551±20	1 557±24	1 505±20	1 515±24

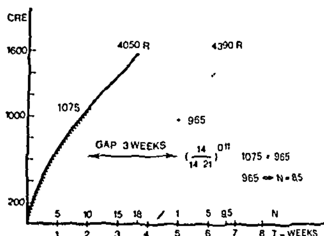
Then the number of fractions equivalent to CRE (II) will be

$$965 = 0\,97 \times 1\,10 \times 225 \times N^{0\,65} \quad N = 8\,5 \tag{4}$$

That is, CRE 980 corresponds to 8 5 × 225 R with 5 treatments per week From the calculation for the right field it is known that 18 fractions give CRE 1 575 (eq 1) Therefore after the gap on the left field 18 − 8 5 = 9 5 fractions more are necessary The total exposure was 4 390 R and treatment time 47 days Thus a gap of 3 weeks has been compensated with 340 R equal to 8 per cent of the exposure

The biologic effect of the irradiation was estimated by measuring the skin erythema and pigmentation Both were recorded by means of a photoelectric reflexion meter (Photovolt, Model 670) An area of approximately 2 5 cm² was illuminated with light of wavelength 578 nm Light of this wavelength is absorbed by oxyhemoglobin The reflected light was read (in scale divisions) The increase of pigmentation resulting fom the irradiation was registered in the same manner but with light of wavelengths above 660 nm Measurements were performed twice weekly, commencing before the first treatment, at 6 points numbered 1 to 6 (Fig 1) In addition, the patients were photographed at least once a week

In connection with each irradiation TLD determinations were performed including determinations at points 1 to 6 which were used for reflectance measurements



[illegible] with a gap of 3 weeks after 10 fractions

(HVL 1.2 mm Cu, exposure rate 80 R/min), the reference point for exposure is the centre of the field at the skin surface. The exposure rate at this point has been determinated by the National Institute of Radiation Protection, Stockholm. Relative exposure determinations have been performed with a Baldwin Farmer ionization chamber with half the sensitive volume lowered into a masonite phantom. To convert the exposure in R to absorbed dose in rad the f factor 0.94 rad/R was used. Further a RBE correction of 1.17 in relation to ^{60}Co radiation was used in the calculations of CRE, i.e. 1 R (HVL 1.2 mm Cu) corresponds to 1.10 rad (^{60}Co). The fractionation schedule was 5×225 R per week on both fields. The two treatment schedules are presented in Fig. 1. All patients were treated identically no matter whether the patients were operated upon the left or the right side.

The intention was to administer a CRE value of about 1 575 for each field. The number of fractions and the total dose to obtain this effect was calculated as follows (Fig. 2).

$$\text{Right field: } 1\,575 = 0.97 \times 1.10 \times 225 \times N^{0.65} \qquad (1)$$

$$N = 18$$

where 0.97 approximately corresponds to $(T/N)^{-0.11}$ for 5 treatments per week. The total exposure was therefore 4 050 R and the treatment time 24 days.

Left field. The effect of the first 10 fractions within a fortnight is

$$\text{CRE (I)} = 0.97 \times 1.10 \times 225 \times 10^{0.65} \qquad (2)$$

$$\text{CRE (I)} = 1\,075$$

After a gap of three weeks this value is reduced to

$$\text{CRE (II)} = \left(\frac{14}{14+21}\right)^{0.11} \times 1\,075 \qquad (3)$$

$$\text{CRE (II)} = 965$$

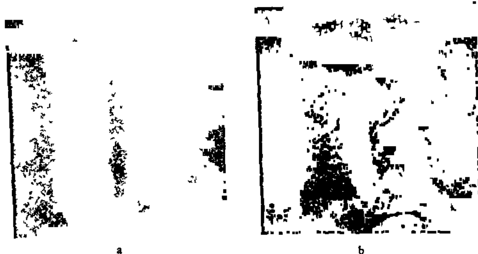


Fig 3 Maximum skin reactions in a patient after CRE 1 585 a) Right field 5 × 225 R per week, totally 4 050 R b) Left field 5 × 225 R per week, a gap of 3 weeks after 10 fractions, totally 4 390 R

Table 2

Mean values and total means (in per cent) of exposure measured with TLD for the 10 patients in the '5 per cent series' according to measurement points 1 to 6 (95 per cent confidence)

Patient No	Measurement point					
	1	2	3	4	5	6
1	97 7±6 1	95 5±3 2	98 8±4 7	100 0±3 1	95 6±4 0	100 1±3 0
2	100 1±2 3	101 6±3 4	98 7±3 2	100 2±2 7	96 2±2 6	98 4±3 0
3	97 8±2 8	97 0±3 2	98 1±2 8	98 4±2 7	92 6±2 8	97 8±2 6
4	97 1±4 0	95 9±3 6	98 4±3 8	97 7±3 5	92 9±4 3	97 7±2 7
5	91 9±4 3	93 9±3 2	97 3±2 7	96 8±2 6	93 9±2 8	95 9±3 2
6	94 9±1 8	96 6±3 0	94 5±2 9	97 4±2 6	92 0±2 9	94 4±3 0
7	96 1±2 2	98 8±3 2	95 8±2 1	97 4±2 1	93 4±3 0	96 4±3 0
8	94 0±3 7	97 0±5 0	97 8±2 6	98 8±3 5	96 5±3 0	98 0±3 4
9	92 9±3 5	96 9±3 0	97 7±3 6	97 3±3 5	97 0±4 6	96 3±3 5
10	91 5±3 0	96 9±3 0	94 8±3 8	98 2±3 2	93 8±3 3	94 5±3 1
Total mean	95 4±2 0	97 0±1 5	97 2±1 1	98 3±1 0	94 4±1 3	97 0±1 3

Table 3

Exposure difference, CRE and CRE difference between the two fields, calculated from the TLD determinations in Table 2 and the final exposure to each field (mean values and 95 per cent confidence)

	Measurement point					
	1	2	3	4	5	6
Exposure (R)	16 × 237	15 5 × 225 (mean)	16 × 237	15 5 × 225 (mean)	16 × 237	15 5 × 225 (mean)
Exposure diff according to TLD (%)	6 9		7 5		5 9	
CRE	1 495±30	1 410±20	1 525+15	1 430+20	1 480+20	1 410±20
CRE difference (%)	6 0		6 6		5 0	

(LINDSKOUG 1975) The relative exposure difference between the two fields for each patient proved to be small and practically negligible (Table 1) The mean value of the average exposures for all patients was also calculated (Table 1) The daily TLD-determinations were considered as a control of the relative exposure difference between the two fields for each patient and between all the patients

Some of the first 7 patients developed bilaterally a slightly exudative desquamation in a part of the irradiated area which healed within a week During this period the spectrophotometer measurements were unsatisfactory To avoid this, the exposure

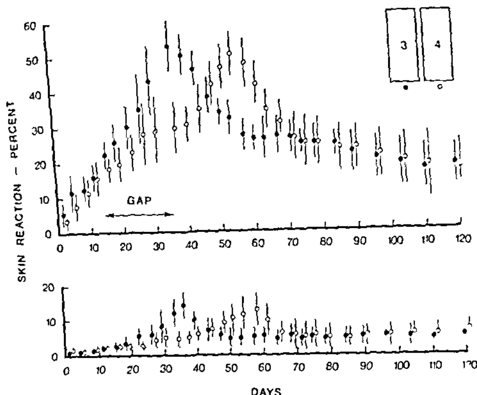


Fig. 5 Mean values of the erythema and pigmentation measurements in the middle parasternal region of the same patients as in Fig. 4 Measurement points 3 and 4 Upper diagram Erythema. Lower diagram Pigmentation ○ with gap ● without gap

the two treatment courses The time for maximum reactions in the different areas is given in Table 5 The maximum reaction developed somewhat earlier in the upper region as compared with the lower one, which was also noticed in the previous investigation

Table 5

Time for maximum skin reactions in the gap series after start of irradiation (mean and 95 per cent confidence)

	Measurement point					
	Right field			Left field		
	1	3	5	2	4	6
Treatment time (days)		24±1			49±1	
Erythema	38±2	39±2	41±3	54±3	55±3	55±2
Pigmentation	38±2	40±3	40±3	55±3	56±3	57±2

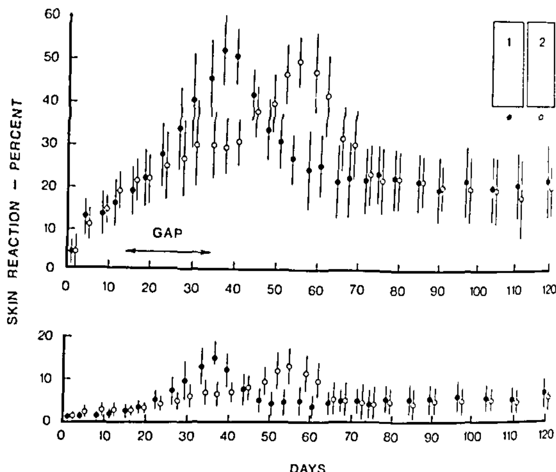


Fig 4 Mean values of reflectance spectrophotometer measurements (per cent of pre irradiation value) for erythema (wavelength 578 nm) and pigmentation (wavelength 660 nm) of the 14 patients in the 'gap series Measurement points 1 and 2 and fractionation schedules see Fig 1 and text (95% confidence) Upper diagram Erythema Lower diagram Pigmentation ○ with gap ● without gap

reaction on the side treated with gap but in the others no differences in the skin reactions could be observed between the right and left sides

The moist skin reactions in these patients were slight They developed only in a small part of the irradiated areas and healed in all cases within a week The maximum reactions in a patient after CRE 1 585 for each field, are illustrated in Fig 3

The reflectance determinations at the 6 measurement points were analyzed separately for each patient The change in the reflectance values during the period of treatment and the follow-up was normalized to the initial values for non-irradiated skin In Table 4 the mean values of the initial measurements for all patients are presented *The slightly increased values in the lower part of the parasternal region* (points 5 and 6) are caused by the higher sympathetic tone in this region (ADAMS-RAY 1952)

The results of the reflectance determinations for all patients appear in Figs 4 to 6, which illustrate the development of skin erythema and pigmentation during and after

Table 7

Mean values of spectrophotometric pigmentation measurements in the 'gap series' at maximum, 4 days before and after maximum (95 per cent confidence)

Radiation induced pigmentation (per cent of preirradiation values)	Measurement point					
	1	2	3	4	5	6
4 days before maximum	14 6±4 4	11 2±3 6	12 9±3 6	11 0±3 9	9 6±2.7	8 9±4 5
Maximum	17 6±3 1	13 5±3 2	13 5±3 6	12 1±4 0	14 4±3 6	12 0±4 0
4 days after maximum	8 6±3 2	9 5±5 4	8 9±3 9	10 6±4 6	9 5±3.3	10 0±4 4

Table 8

Mean values of spectrophotometric measurements in the '5 per cent series' before irradiation, and at maximum reactions (95 per cent confidence) Right field 5 × 237 R/week, totally 3 790 R/22 days (measurement points 1, 3, 5) Left field 5 × 225 R/week, totally 3 600 R/22 days (measurement points 2 4 6) Time for maximum skin reactions (mean and 95 per cent confidence)

		Measurement point					
		1	2	3	4	5	6
Pre irradiation value (reflectance in scale divisions)	Erythema	24 9±2 1	26 9±3 8	28 3±3 7	30 0±4 3	32.7±3 2	32 7±4 8
	Pigmentation	53 7±2 0	54 5±2 2	55 9±2.0	56 3±2 0	57 9±1 9	57 7±1 8
Maximum skin reaction (per cent of preirradiation value)	Erythema	48.5±3 7	42 7±7 4	49 6±5 1	46 6±4 7	46 7±6 0	40 0±7 1
	Pigmentation	16 5±3 2	15 3±3 1	15 9±3 4	15 5±3 4	13 5±4 1	11 7±3 0
Days after start of irradiation for maximum skin reaction	Erythema	36 ±2	35 ±2	37 ±2	38 ±2	39 ±2	41 ±3
	Pigmentation	37 ±3	37 ±2	38 ±3	40 ±3	40 ±2	42 ±3

ment course if the maximum is not to be overlooked Further statistical analysis of the erythema measurements indicates that for a gap of 3 weeks a compensation of 8 per cent of the exposure applied in this schedule was adequate, except for the pigmentation in the upper parasternal region (points 1 and 2) Here the pigmentation was less marked in the 'gap treated' area

The result from 10 patient irradiated on both parasternal fields, where the prescribed exposure difference was 5 per cent, is summarised in Table 8 By reflectance determination the effect of an exposure difference of 6 to 7 per cent could be measured to a 5 per cent significant level for skin erythema, but not for pigmentation Visually, the difference in erythema between the fields was obvious at maximum reaction for all the patients (Fig 7)

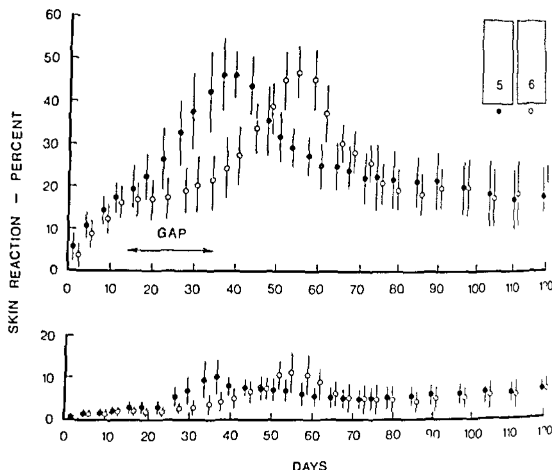


Fig 6 Mean values of the erythema and pigmentation measurements in the lower parasternal region of the same patients as in Fig 4 Measurement points 5 and 6 Upper diagram Erythema Lower diagram Pigmentation ○ with gap ● without gap

The mean values of the spectrophotometric measurements at maximum, as well as 4 days before and after the occurrence of maximum skin reaction are presented in Tables 6 and 7 They demonstrate the short duration of the maximum skin reaction and the necessity of frequent controls of the reaction after the end of the treat

Table 6

Mean values of spectrophotometric erythema measurements in the gap series at maximum 4 days before and after maximum (95 per cent confidence)

Radiation induced erythema (% of pre irradiation value)	Measurement point 1	2	3	4	5	6
4 days before maximum	47.0±5.6	46.0±5.9	48.2+5.8	46.6±5.1	43.5+5.9	43.6±4.8
Maximum	56.0+4.1	53.0±4.2	57.2±4.5	53.2+4.6	50.6+5.6	51.3±5.0
4 days after maximum	43.9+5.5	46.8+8.4	45.6+5.1	42.7±5.5	44.1±6.1	43.6±6.8

Table 7

Mean values of spectrophotometric pigmentation measurements in the 'gap series' at maximum, 4 days before and after maximum (95 per cent confidence)

Radiation induced pigmentation (per cent of preirradiation values)	Measurement point					
	1	2	3	4	5	6
4 days before maximum	14.6±4.4	11.2±3.6	12.9±3.6	11.0±3.9	9.6±2.7	8.9±4.5
Maximum	17.6±3.1	13.5±3.2	13.5±3.6	12.1±4.0	14.4±3.6	12.0±4.0
4 days after maximum	8.6±3.2	9.5±5.4	8.9±3.9	10.6±4.6	9.5±3.3	10.0±4.4

Table 8

Mean values of spectrophotometric measurements in the '5 per cent series' before irradiation, and at maximum reactions (95 per cent confidence) Right field 5 × 237 R/week, totally 3 790 R 22 days (measurement points 1, 3, 5) Left field 5 × 225 R/week, totally 3 600 R/22 days (measurement points 2, 4, 6) Time for maximum skin reactions (mean and 95 per cent confidence)

		Measurement point					
		1	2	3	4	5	6
Pre-irradiation value (reflectance in scale divisions)	Erythema	24.9±2.1	26.9±3.8	28.3+3.7	30.0+4.3	32.7±3.2	32.7±4.8
	Pigmentation	53.7±2.0	54.5±2.2	55.9±2.0	56.3±2.0	57.9±1.9	57.7±1.8
Maximum skin reaction (per cent of preirradiation value)	*Erythema*	48.5±3.7	42.7±7.4	49.6±5.1	46.6+4.7	46.7±6.0	40.0±7.1
	Pigmentation	16.5±3.2	15.3±3.1	15.9+3.4	15.5+3.4	13.5±4.1	11.7±3.0
Days after start of irradiation for maximum skin reaction	Erythema	36 ±2	35 ±2	37 ±2	38 ±2	39 ±2	41 ±3
	Pigmentation	37 ±3	37 ±2	38 ±3	40 ±3	40 ±2	42 ±3

ment course if the maximum is not to be overlooked Further statistical analysis of the erythema measurements indicates that for a gap of 3 weeks a compensation of 8 per cent of the exposure applied in this schedule was adequate, except for the pigmentation in the upper parasternal region (points 1 and 2) Here the pigmentation was less marked in the 'gap treated' area

The result from 10 patient irradiated on both parasternal fields, where the prescribed exposure difference was 5 per cent, is summarised in Table 8 By reflectance determination the effect of an exposure difference of 6 to 7 per cent could be measured to a 5 per cent significant level for skin erythema, but not for pigmentation Visually, the difference in erythema between the fields was obvious at maximum reaction for all the patients (Fig 7).

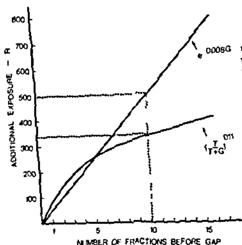


Fig 8

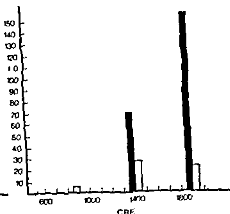


Fig. 9

Fig. 8 Depending upon the position of the gap varying compensation for a gap of 3 weeks in a treatment course with 5 × 225 R per week, calculated with the corrections proposed by ELLIS and KIRK et coll Additional exposure after N = 10 weeks ELLIS 340 R (8 %), totally 4 390 R KIRK et coll 500 R (12 %) totally 4 550 R

Fig 9 The repopulation rate defined as the dose increment (rad/day) necessary to counteract repopulation of epidermal cells during the first and second week after different radiation injury expressed in CRE ■ first □ second week after CRE 850, 1 400 and 1 900

ference in human skin reaction in 80 per cent of the cases, when the reactions were scored visually by a special code

The accuracy of this investigation of ELLIS' gap correction was analysed by comparing the differences in mean values of the maximum skin reactions between each field of the 'gap series' (Tables 6, 7) and the '5 % series' (Table 8) In the latter the skin erythema was significantly different in the upper and lower region, where the exposure differences were 7 and 6 per cent, respectively The differences between maximum reactions in the '5 % series' are evidently higher than the differences in the field with and without a gap of 3 weeks Pigmentation is a less sensitive parameter and is not good enough for measuring the accuracy of such a small gap-correction in this case

For the gap-correction $(T/T+G)^{0.11}$ it is evident that the duration of the gap (G days) and the treatment time (T days) before gap determine the size of the dose compensation But from further knowledge of the CRE formula it can be proved that the additional dose also depends on the fractionation schedule before and after gap and the definition of additional dose (KIRK, personal communication) The additional dose was defined with the presumption that after gap, treatment is resumed at the same dose per fraction as before the gap, but with a greater number of fractions and a correspondingly increased time This definition differs from that adopted by

to 20 hours) in order to return to the normal value when the basal cell population approaches its original size during the second week

In marked contrast to the basal cells, the less proliferative connective and vascular tissue compartments of skin present very low proliferative response to irradiation injury TANNOCK & HAYASHI (1972) have reported that the rate of the endothelial cell division is slow even after rather high doses of radiation Also the split-dose experiments concerning inhibition of callus formation by HAYASHI & SUIT (1972) with gaps of 1 and 4 weeks after a single dose of 1 000 rad indicated hardly any repopulation of connective vascular tissues

Thus for a gap late in a treatment course the dose compensation according to KIRK is probably more relevant especially for cell compartments with potentially high proliferative capacity Where late radiation effects are concerned, the vascular injury is considered most important, therefore the gap-correction proposed by ELLIS may be more suitable

Acknowledgements

We are very grateful to Mrs S Benner for helping us with the spectrophotometer measurements and to the medical photographer O Roos

SUMMARY

In patients with mammary carcinoma, irradiated postoperatively on the parasternal regions prospective dose calculations for different fractionation schedules have been per-
ue was recorded
he right side re-
weeks A com-
8 per cent of the total exposure was found to be adequate The smallest exposure difference that could be clearly discriminated visually and with spectrophotometry was recorded in a special series and was found to be 6 to 7 per cent

ZUSAMMENFASSUNG

Prospektive Dosisberechungen fur verschiedene Fraktionierungsschemata mit der CRE-Formel wurden bei Patienten mit einem Mammakarzinom, die postoperativ parasternal bestrahlt wurden vorgenommen Der biologische Strahleneffekt fur Normalgewebe
mittels Reflektionsspektroph
Die rechte Seite erhielt
Aufenthalt von 3 Wocher
Gesamtdosis fur den Auf
die visuell und spektrophotometrisch eindeutig war. Die geringste Differenz in der Bestrahlung, untersucht diese betrug 6 bis 7 Prozent wurde in einer besonderen Serie

KIRK et coll (1974), who compensate for a gap by increasing the dose per fraction after gap instead of the number of fractions

The additional exposure for a gap of 3 weeks is calculated and plotted in Fig 8 as a function of the number of fractions before gap for the fractionation schedule 5 × 225 R per week These calculations may be performed with a simplified expression for the procedure described in eqs 2 to 4 The exposure compensation is then equal to $(1-(T/T+G)^{0.169}) \times D$ where D is the total exposure before gap, T and G as above This formula is only valid when the fractionation schedule is the same before and after the gap

In Fig 8 also the additional exposure for a gap of 3 weeks calculated with the gap-correction $e^{-0.008G}$, is plotted as a function of the number of fractions before gap for 5 × 225 R per week This gap-correction is handled in the same way as the other one described in eqs 2 to 4 The corresponding simplification for calculation of the additional exposure is $(1-e^{-0.012G}) \times D$, G and D as above

A generalized form of the expressions is

$$\frac{d_2}{d_1} \times \left(\frac{\varrho_1}{\varrho_2}\frac{d_1}{d_2}\right)^{1.54} \times \left[1-\left(\frac{T}{T+G}\right)^{0.169}\right] \times D \tag{5}$$

and the same for $(1-e^{-0.012G}) \times D$, where d_1 and d_2 are the dose per fraction before and after gap, and ϱ_1 and ϱ_2 are equal to $(T/N)^{-0.11}$ before and after gap

A comparison of these functions for a gap of 3 weeks after 10 fractions indicates additional exposures of 340 R and 500 R, respectively These compensations imply only a difference of 4 per cent in the total exposure for the required CRE value Any difference in biologic effect of such a small exposure difference may not be discriminated by the reflectance spectrophotometer technique For the fractionation schedule used and with a gap of 3 weeks in the treatment course before 11 fractions have been given, i e after a CRE value of about 1 100, both corrections may be used without any significant difference in result and there is no evidence to prefer one correction to the other

However, the discrepancy increases between the two corrections with increasing exposure or radiation effect before the gap starts Exposure compensation for a gap after high exposures may vary much more than after moderate exposures, because different tissues have varying potential ability to proliferate

DENEKAMP (1973) has shown that cell-killing by irradiation induces a change in the rate of repopulation of epidermal cells in the feet of mice By microscopic observation of the radiation effect on skin at some specified level the proliferation rate was estimated and expressed as the dose increment (rad/day) necessary to counteract repopulation of the basal cells Data evaluated by DENEKAMP on the repopulation during the first and second week after 4, 9 and 14 daily fractions of 350 rad (equivalent to ^{60}Co) are presented in Fig 9 These doses correspond to CRE values 850, 1 400 and 1 900, respectively When an appreciable amount of injury has been accumulated (CRE 1 900) the cycle time was considerably reduced (from about 5 days

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RADIATION SENSITIVITY OF LYMPHOCYTES FROM HUMAN BLOOD AND FROM THE THORACIC DUCT

J EDGREN and T H WEBER

The role of the lymphocyte in various immunologic reactions has been greatly clarified during the last ten years (GOWANS & MCGREGOR 1965, WEGELIUS et coll 1970) The central role of the lymphocytes in cell mediated immunologic reactions such as transplantation immunity has led to attempts to control or reduce their activity by various methods One way is to use ionizing radiation Lymphocytes are quite sensitive to radiation and irradiation has therefore been used in connection with organ transplantation to cause immunosuppression (ROSENGREN & SKÖLDBORN 1968) The irradiation is directed either towards a limited site in order to achieve local immunosuppression or towards lymphoid tissues or peripheral blood lymphocytes to achieve a more generalized effect Analysis of the lymphocyte function after irradiation provides methods for the evaluation of the immunosuppressive effect of therapy and might also under certain circumstances be used as a biologic radiation dosimeter (ILBERY et coll 1971)

The present investigation was undertaken to evaluate the radiation sensitivity of blood and thoracic duct lymphocytes and to investigate the possibility of using the lymphocyte function for evaluating the effects of extracorporeal irradiation of lymphatic cells

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RÉSUMÉ

Les auteurs ont effectué avec la formule CRE des calculs de dose prospective pour différents plans de fractionnement chez des malades atteintes de cancer du sein et soumises à une irradiation post-opératoire des régions parasternales L'effet biologique des radiations sur le tissu normal a été mesuré par spectrophotométrie de réflectance de l'érythème cutané et de la pigmentation Le côté droit a reçu 4 050 R en 25 jours, le coté gauche 4 390 R en 47 jours avec un intervalle de 3 semaines Les auteurs ont trouvé qu'une compensation par 8 pour cent de l'exposition totale était convenable pour cet intervalle Sur une série spéciale ils ont mesuré la plus petite différence d'exposition nettement décelable visuellement et par spectrophotométrie et l'ont trouvée égale à 6 à 7 pour cent

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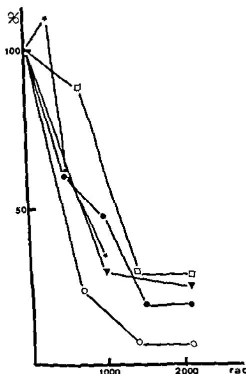


Fig. 1 Effect of irradiation on the function of peripheral blood lymphocytes from 5 subjects. Incorporation of ^{125}I-deoxy uridine into DNA of lymphocytes stimulated with 10 μg ml kidney bean LA The incorporation into non-irradiated lymphocytes was taken as 100 per cent. Abscissa radiation dose in rad Ordinate incorporation into lymphocytes (in per cent).

resistant lymphocyte population existed, a different dose response curve could be expected for these cells than for the whole population On the other hand, if the incorporation of radiation activity was decreased in all cells after irradiation, similar dose response curves for treated and untreated cells would be expected The results appear in Fig 2 One cell population reacted to very low doses of LA in vitro With increasing doses of LA more and more cells were activated However, after irradiation with 2 800 rad, the cells activated by high doses of LA were eliminated and only the cells reacting to low doses remained These cells appeared to be very resistant and the response was essentially similar in cells irradiated with 2 800 rad and in untreated cells This clearly indicates that there is a lymphocyte population characterized by high sensitivity to stimulation by lectins and high resistance to radiation The exact function and nature of this population is not known, but the reason for the low sensitivity to radiation might be the fact that before radiation certain metabolic reactions had occurred in these cells, reactions which are easily disturbed in other cells and which are required during lymphocyte activation in vitro The possibility of the existance of what is called 'preactivated lymphocytes in blood has previously been suggested One feature of a pre activated cell is that it has performed at least some RNA synthesis and that it is very sensitive to stimulation by lectins (WEBER et coll 1974)

Material and Methods

Lymphocytes were collected from peripheral blood of 5 healthy subjects and by cannulation of the thoracic duct from 2 patients with rheumatoid arthritis. The blood lymphocytes were isolated and purified as described previously (LINDAHL-KIESSLING 1972), except that the carbonyl-iron treatment of the blood was omitted The thoracic duct lymphocytes were purified by washing three times in culture medium

The cells were irradiated at room temperature before isolation from blood or lymph, immediately after collection of the samples A dose rate of 220 rad/min, 250 kV, 15 mA and a filtration of 1 mm Cu, was used

Cell cultures were performed in triplicate by suspending 0 5 or 1 0 × 10^6 lympho cytes in 2 ml Eagle's minimum essential medium supplemented with l-glutamine and 10 % pooled, inactivated, human AB-serum, in 16 mm × 125 mm polycarbonate tubes The cultures were incubated for 66 hours in a humidified 5 % CO_2 in air atmos phere, 18 hours before termination 1 μCi ^{125}I-deoxy-uridine was added The cultures were terminated by washing the cells twice in ice-cold saline, and the activity was counted in a well-type scintillation counter.

Lymphocytes were activated by adding to the cultures doses of 0 5 to 10 μg/ml kidney bean leucoagglutinin (LA) purified as described by RÄSÄNEN et coll (1973) and prepared at Medix Labs Ltd , Helsinki, Finland

Details of the 2 patients will be reported elsewhere (EDGREN et coll 1976) In brief, they were subjected to thoracic duct cannulation and the lymphocytes drained were irradiated with 2 800 rad and returned to the patients by intravenous infusion Duct drainage was continued for 14 and 18 days, respectively, during which time 24 and 29 l of lymph were collected, irradiated and reinfused, except 2 l which were used for cell cultures and other investigations The lymph contained a mean of 4 5 × 10^9 and 3 × 10^9 lymphocytes/l Cell cultures were made from peripheral blood of the patients before drainage and 1 and 2 to 3 weeks after the beginning of the treatment

Results and Discussion

The effect of irradiation of peripheral blood lymphocytes appears in Fig 1 At 1 000 rad, at least a 50 per cent decrease was obtained in the ability of the lymphocytes to incorporate ^{125}I-deoxy-uridine after stimulation with LA in vitro However, with higher doses a plateau was reached and the in vitro response of lymphocytes was not even abolished with 2 800 rad This could be due either to a very resistant lymphocyte population or to a diminished incorporation of deoxy-uridine into all lymphocytes

It is known that lymphocytes become either totally activated with lectins or not at all, never only partly activated, i e in a given single cell the response to stimulation is zero or maximum (HANDMAKER et coll 1969) In order to resolve these alternatives, the response of irradiated lymphocytes to varying doses of LA was examined If a

SUMMARY

Peripheral blood and thoracic duct lymphocytes are sensitive to irradiation However, a distinct population of resistant lymphocytes exists, which is characterized by reactivity to very low doses of lymphocyte stimulating lectins in vitro Blood lymphocytes are rapidly eliminated from the circulation after radiation damage An analysis of the function of blood lymphocytes is thus of little or no use in assessing the therapeutic effect of extracorporeal irradiation Lymphocyte activation must accordingly also be unsuitable for use as a biologic dosimeter after accidental total body irradiation

ZUSAMMENFASSUNG

Das periphere Blut und die Lymphozyten des Ductus thoracicus sind gegenuber Bestrahlung empfindlich Es liegt jedoch eine distinkte Population resistenter Lymphozyten vor, die sich durch ihre Reaktivität gegenuber sehr niedrigen Dosen von Lymphozyten stimulierenden Lectinen in vitro auszeichnen Blut Lymphozyten werden nach einer Schädigung durch Strahlung rasch aus der Zirkulation entfernt Eine Analyse der Funktion von Blut Lymphozyten ist deshalb von geringem oder keinem Wert bei der Feststellung des therapeutischen Effekts der extracorporalen Bestrahlung Die Aktivierung von Lymphozyten muss deshalb auch als biologisches Dosimeter nach accidentellen Gesamtkorperbestrahlung unanwendbar sein

RÉSUMÉ

Les l[illegible]
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lymp[illegible] éliminés de la circulation après les lésions dues aux radiations L'étude de la fonction des lymphocytes sanguins est donc de peu d intéret ou sans intérêt pour apprécier l effet therapeutique de l irradiation extracorporéale L'activation lymphocytaire doit donc aussi ne pas convenir comme dosimètre biologique après une irradiation accidentelle de tout le corps

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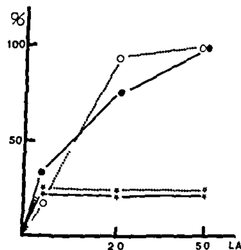


Fig 2 Dose response (in per cent) of irradiated (2 800 rad) and non irradiated thoracic duct lymphocytes from 2 subjects to different doses of kidney been LA (μg/ml) The two upper curves non irradiated cells, the lower curves irradiated cells

No significant alteration of the function of the lymphocytes from peripheral blood of the patients subjected to extracorporeal irradiation of thoracic duct lymphocytes was found If the stimulation is expressed as an index obtained by dividing the counts of stimulated cultures with counts of unstimulated cultures, the mean of the results from two patients was before extracorporeal irradiation 14 (range 11–16), after one week of thoracic duct drainage and irradiation 13 (range 11–16), and after the completion of thoracic duct drainage and irradiation, i e 2 to 3 weeks after the beginning of the treatment, 12 (range 8–17) This absence of significant alterations is most likely due to the rapid elimination of irradiated lymphocytes from peripheral blood It has been shown that lymphocytes damaged by radiation remain in the peripheral blood for a mean of only 2 min (FIELD et coll 1972) This makes it impossible to use peripheral lymphocytes as a measure of the effect of extracorporeal irradiation of blood or lymph, although it has been claimed in one report that this treatment causes a depression of peripheral lymphocyte activation (ROSENGREN et coll 1968) The view that the irradiated lymphocytes are rapidly eliminated from peripheral blood is also supported by the fact that no irradiation-induced chromosomal aberrations were seen in the blood lymphocytes of these patients (EDGREN et coll) In one of the patients, scanning of ^{51}Cr-labelled irradiated lymphocytes was performed and a definite uptake in the spleen was demonstrated, which indicates that the reticuloendothelial system eliminates the damaged cells from the circulation (EDGREN et coll, FIELD et coll)

It may also be concluded that an analysis of lymphocyte activation after accidental total body irradiation is not suitable for evaluating the radiation dose, because the lymphocytes seem to react only at doses which are lethal and also because pre-irradiation controls are lacking Thus the only reliable method for biologic dosimetry based on the use of peripheral blood cells is the time-consuming method employing chromosomal analysis (EVANS 1972)

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MEASUREMENTS OF SINGLE EVENT SPECTRA WITH A WALL-LESS PROPORTIONAL COUNTER IN LOW LET RADIATION FIELDS

K A JESSEN

It is generally accepted that knowledge of the distributions of energy absorbed by microscopic sites is necessary for the understanding of the response of a cell exposed to radiation The technique for measuring such distributions has been introduced several years ago (ROSSI & ROSENZWEIG 1955) The measurements are normally performed by simulating microscopic volumes with tissue equivalent gases at low pressure in proportional counters with walls of tissue equivalent materials

Measurements in low LET radiation fields of high energy roentgen and gamma rays have been scarce especially in fields for radiation therapy (LINDBORG 1974) Two of the main problems in measuring distributions in radiation fields are the high photon fluences and the wall effects in the detector

Measurements of single event distributions have been performed with a wall less dipole proportional counter in ^{60}Co *gamma ray fields* from a point source and in collimated roentgen ray fields from a 6 MV Varian linear accelerator, and the results are now reported

The probability distributions in event sizes P(Y) are measured in these fields at gas pressures which simulate spheres with diameters of 0 4 μm, 1 μm, and 2 μm tissue The event size Y is defined as the quotient of energy deposited by an event ε in a

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of silver on the outside The potential of the guard electrode is adjusted so that the silver layer on the hemispherical cup fits an equipotential surface of the dipole field The potential of the guard electrode is about 20 per cent of the anode potential The two critical parameters, the position of the anode in the guard cup and the potential of the guard electrode, were optimized by using a collimated beam of 5 3 MV α particles from an open ^{210}Po source The collimated α beam was crossing the detector along different diameters for checking the spherical collecting volume Due to the rotational symmetry about the axis defined by the supports of the electrodes investigations are only performed in one of the plans containing this axis The α source was placed on a median up to $\pm 60°$ from the central diameter between the electrodes and deviations in the measured pulse high were less than ± 6 per cent The electrode supports are fixed to perspex sockets for alignments

The vacuum chamber system The vacuum chamber is a 75×10^{-3} m^3 cylindrical container of stainless steel and with a diameter of 0 4 m On the end flanges are mounted perspex windows (thickness 5–20 mm) for exposure to external sources As counting gas is used a tissue equivalent gas mixture composed by volume of 64 4 per cent CH_4, 32 4 per cent CO_2, and 3 2 per cent N_2 The counter is operated with a gas flow down to 30 mm$^3 \times$ s^{-1} (atmospheric) The design of the gas flow system is schematically represented in Fig 1 To maintain a constant and low pressure in the chamber, an electromagnetic valve (Balzer RME010 and valve control unit RVG040) is inserted between the gas container and the chamber The valve is controlled by a pirani gauge (Balzer TPR010) which measures the pressure in the chamber For controlling the absolute pressure and the gas dependency of the pirani at higher pressure, a mercury manometer is used (Struers USA manometer) For reducing the gas flow rate a needle valve is employed between the chamber and the foreline traps for the rotary pump (Balzer DUO008) During all measurements the pressure was constant within 0 2 per cent The rotary pump was mechanically separated from the chamber system for neutralizing vibrations at the electrodes which considerably reduced the electronic noise level

Electronics The counter was connected directly to a charge sensitive preamplifier (ORTEC 109PC) with a short cabel The capacity of the cabel and the detector is 25 pF which gives a noise level of about 450 e_{rms} The limiting effect of the electronic noise is defined by the root mean square (rms) of electrons which represent the preamplifier noise The signals are then fed to a linear amplifier (ORTEC 452) with pulse shaping facilities Normally a bipolar pulse shaping and a shaping time constant of 3 μs are used Finally, the pulses were fed to the ADC of a multichannel analyzer (Northern Scientific, 4096 channels) The linearity of the electronic system was checked with a precision pulser

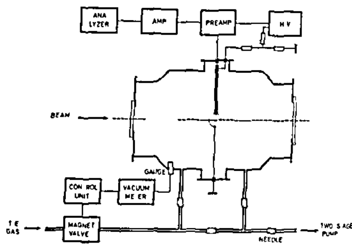


Fig 1 The experimental arrangement (not in scale)

spherical volume of *diameter d by d*, $Y = \varepsilon/d$ Also *energy deposition spectra* are presented for the two radiation qualities The deviations in these spectra are not *sufficient for conclusions* about significant differences in microscopic energy deposition for the two qualities, taking the differences in the measuring geometries into account

Calculations of the relative variance in LET are performed for the radiation sources used and for different cut-off energies corresponding to different diameters or cord lengths in the detector These values are compared with the relative variance of the measured distributions which shows that only for small sites the LET part in the variance could be greater than the contribution from the straggling

Description of the apparatus

The detector The experimental arrangement is illustrated schematically in Fig 1 The wall-less proportional counter used is a so called martini counter (GLASS & BRABY 1969), whose boundaries are determined by a spherically shaped electric field *This field is performed by two exactly spherical electrodes of stainless steel,* 0 8 mm in diameter (SKF balls) The electrodes are supported by two cannula pipes *of stainless steel and with an outer diameter of 0 42 mm The counter cathode is* connected to ground potential and the anode is connected to a high voltage supply, *working in the potential range 700 V to 1 100 V, depending on the gas pressure used* The potential should be sufficiently high to get reasonable gas multiplication ($\approx 10^4$) and *homogeneous collection of the free electrons formed in the spherical volume* without recombination, and well below the limit for breakdown of the counting gas The separation between the two electrodes is *20* mm

For defining the spherical shape the collecting volume for electrons is limited by a guard electrode This electrode consists of a *glass pipe containing the anode support* and ending in a hemispherical cup with a diameter of 2 5 mm and with the anode placed at the center The glass pipe is coated *and made conductive with a thin layer*

The energy calibration is performed by using the beam of α particles for the three gas pressures applied, simulating volumes with diameters of 0 5 μm, 1 μm, and 2 μm tissue The energies of the α particles at the center of the detector and the energy losses in the three simulated volumes were calculated following tables given by BARKAS & BERGER

The calibration was tested for lower energies using a ^{55}Fe source placed near to the detector and producing photoelectrons at 5 88 keV in the counting gas This test could only be performed with a gas pressure higher than used in the measurements ($>10^4$ N m^{-2}) because the range of the photoelectrons should be less than the simulated volume to get a reasonable peak This test was performed with a gas pressure at 10^4 N m^{-2} simulating about 2 μm tissue and yielded an energy deposition of 122 5 eV per channel compared with 122 7 eV per channel for the α particles, which means an agreement within the experimental uncertainty

The resolution of the detector for ^{55}Fe measured at the high pressure ($\sim 2\ 5 \times 10^4$ N m^{-2}) is about 24 per cent, but the relatively poor resolution of this counter should not be the critical factor in measuring event spectra (KELLERER 1968 a)

Measurements of single event spectra

For measurements of the event spectra for ^{60}Co gamma radiation a point source of 20 MBq ($\sim$0 5 mCi) is placed near to the perspex window (5 mm thick) outside the chamber and in a distance of 0 3 m from the detector Measurements on a ^{60}Co therapy unit was attempted but it was not possible to reduce the photon fluence sufficiently to avoid pile up pulses The background level in the therapy room was also a serious problem when the source was open

For measurements on the linear accelerator, pile up plays an important role, but here it is possible to place the measuring chamber 10 m from the target and with a 1 6 m thick wall of heavy concrete between the target and the detector to reduce the background level below 5 counts per second The pulsed radiation has a frequency of 200 Hz for the dose rate used in these measurements and a pulse length of about 3 μs It is possible to introduce cylindric collimators of lead in both ends of the beam port through the wall for reducing the photon fluence The diameter of the second collimator after the target is constructed in such a way that no interaction with the primary beam passing the first collimator occurs The distance of 4 m between the second collimator and the chamber should prevent collimator effects in the detector Diameters from 6 4 to 1 2 mm was used for the first collimator which gives solid angles from 2×10^{-6} sr to 6×10^{-8} sr for the radiation beam from the target and typical count rates in the detector from 1 000 s^{-1} to 30 s^{-1} This means that only for the smallest collimator the pile up is negligible The chamber is aligned to let the beam pencil cross the detector between the electrodes

It is assumed in the measurements of single event spectra that the size of a pulse from the counter is directly proportional to the number of primary ions formed in an event and thus to the energy deposition in the simulated spherical volume by this

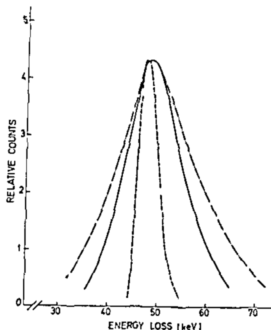


Fig 2

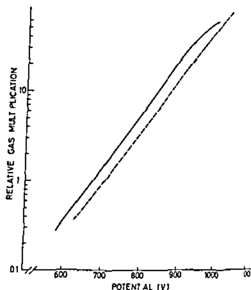


Fig 3

Fig 2 Measured distributions of 5 MeV collimated α particles in 0 5 μm simulated tissue layer for different collimator sizes The beam covers 12 5 per cent (—) and 40 per cent (— —) of the solid angle for the detector volume The dotted line (---) is the Vavilov distribution for a perfectly collimated beam of α particles at the same energy

Fig 3 The relative gas multiplication as a function of anode voltage for two different gas pressures $2\ 67 \times 10^3$ N m^{-2} (—), and $6\ 67 \times 10^3$ N m^{-2} (---)

Calibration and test measurements

For testing, the detector was exposed to 5 3 MeV α-particles from a thin layer of ^{210}Po on a Ni-foil, which gives nearly monoenergetic α-particles The foil was placed in a collimating device 115 mm from the center of the detector and assumed not to disturb the fields in the detector

Two distributions measured after optimizing the spherical field shape appear in Fig 2 The beam of α-particles is covering 12 5 percent and 40 per cent, respectively, of the area of the circle defined by the electrodes and in a plan perpendicularly to the beam As a theoretical limit the Vavilov distribution (SELTZER & BERGER 1964) is also presented in Fig 2 for 5 0 MeV α-particles traversing a thin T E gas layer, simulating 0 5 μm tissue with a calculated energy loss of 48 6 keV (BARKAS & BERGER 1964)

Fig 3 gives the relative gas multiplication as a function of the anode voltage for two typical gas pressures used in the measurements, $2\ 67 \times 10^3$ N m^{-2} (20 torr), and $6\ 67 \times 10^3$ N m^{-2} (50 torr) The pulse height distribution is measured for the α-particles at different voltage The figure illustrates the exponential multiplication in the applied voltage range and the beginning of gas breakdown is suggested only for the low pressure curve

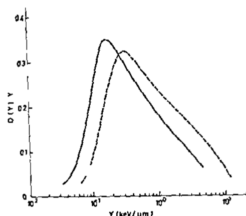


Fig. 5 The energy deposition spectra in 1 µm simulated tissue for 6 MV roentgen radiation (—) and ^{60}Co gamma rays (--)

In Table 1 the absorbed dose and the number averages of event sizes $\overline{Y}_D$, and $\overline{Y}_P$ for the measured event spectra are listed

The agreement between these ^{60}Co data is good, especially for the 2 µm sphere The differences for smaller sites are probably due to greater uncertainties in the data for these sites and not to the wall effect because this effect will contribute to larger event (GLASS & GROSS 1972) The shift for the two radiation qualities is clearly indicated in the data

Comparison with LET values and discussion

It can be shown that for the relative variance V in a measured single event distribution the following relation holds (KELLERER 1968) whenever the particle tracks are long compared to the volume of interest

$V = V_{track} + V_{LET} + V_{track} \cdot V_{LET} + V_{straggling} + V_{gas\ counter}$ V_{track} is the relative variance of the chord length distribution and the value 0.125 is normally used for a spherical volume The other terms are obvious Another relation for the relative variance

Table 1

The number and the dose averages of event sizes $\overline{Y}_P$ and $\overline{Y}_D$ measured for three simulated spheres of tissue in the two radiation fields The figures in parenthesis are data reported by BIAVATI & BOER *V is the relative variance of the single event distributions*

Size (µm)	$\overline{Y}_P$ keV/µm		$\overline{Y}_D$ keV/µm		$V = \frac{\overline{Y}_D}{\overline{Y}_P} - 1$	
	^{60}Co	6 MV	^{60}Co	6 MV	^{60}Co	6 MV
0.5	0.54 (0.496)	0.21	2.32	1.21	3.3	4.6
1.0	0.32 (0.262)	0.18	1.38 (1.240)	0.86	3.3	3.8
2.0	0.24 (0.230)	0.13	1.00 (0.982)	0.64	3.2	4.1

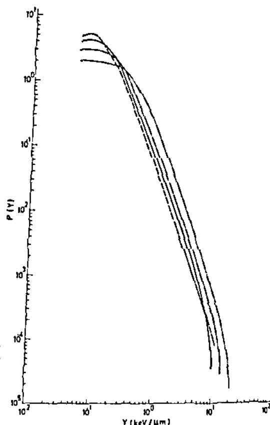


Fig 4 The energy deposition probability curves for ^{60}Co gamma radiation in spheres with simulated diameters of 2 0 μm (—), 1 0 μm (— —), and 0 5 μm (- -) tissue and for 6 MV roentgen radiation in 1 0 μm (---)

event Fig 4 presents the energy deposition probability curves measured for broad gamma beams from the ^{60}Co point source for pressures corresponding to spheres of tissue of 2 0 μm, 1 0 μm, and 0 5 μm in diameter, and for collimated 6 MV roentgen rays at 1 0 μm The results are presented in terms of event size Y, and P(Y) is the normalized probability distribution (KELLERER & ROSSI 1970)

The probability is increasing for larger event sizes as the diameter of the sphere is decreasing This means that the interactions tend to be more definitely alternative for smaller sites, i e more electrons are passing the sphere without any interaction The curve for the 6 MV roentgen rays (Fig 4) reveals that the probability is decreasing for increasing energy of the incoming gamma photons which produce more energetic electrons with lower LET values

Fig 5 illustrates the energy deposition spectra for the two radiation sources in a simulated sphere of 1 μm D(Y) = P(Y) Y is the normalized absorbed dose distribution in event sizes It illustrates the shift in energy deposition for the two sources through lower energy depositions for the 6 MV roentgen rays due to the more energetic electrons The difference in beam geometry would probably also contribute to the deposition shift, especially the influx into the counter volume of δ-electrons with higher deposition events would be of more importance in the broad beam geometry

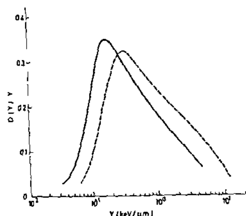


Fig 5 The energy deposition spectra in 1 μm simulated tissue for 6 MV roentgen radiation (—) and ^{60}Co gamma rays (---)

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Table 1

The number and the dose averages of event sizes $\bar{Y}_F$ and $\bar{Y}_D$ measured for three simulated spheres of tissue in the two radiation fields The figures in parenthesis are data reported by BIAVATI & BOER *V is the relative variance of the single event distributions*

Size (μm)	$\bar{Y}_F$ keV/μm ^{60}Co	$\bar{Y}_F$ keV/μm 6 MV	$\bar{Y}_D$ keV/μm ^{60}Co	$\bar{Y}_D$ keV/μm 6 MV	$V = \frac{\bar{Y}_D}{\bar{Y}_F} - 1$ ^{60}Co	$V = \frac{\bar{Y}_D}{\bar{Y}_F} - 1$ 6 MV
0 5	0 54 (0 496)	0 21	2 32	1 21	3 3	4 6
1 0	0 32 (0 262)	0 18	1 38 (1.240)	0 86	3 3	3 8
2.0	0.24 (0.230)	0 13	1 00 (0 982)	0 64	3 2	4 1

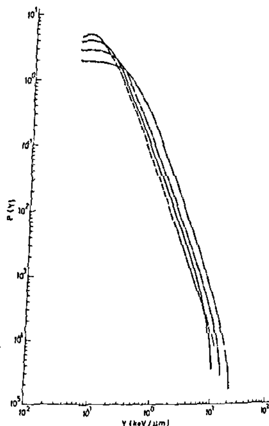


Fig 4 The energy deposition probability curves for ^{60}Co gamma radiation in spheres with simulated diameters of 2 0 μm (—), 1 0 μm (— —), and 0 5 μm (- -) tissue and for 6 MV roentgen radiation in 1 0 μm (---)

event Fig 4 presents the energy deposition probability curves measured for broad gamma beams from the ^{60}Co point source for pressures corresponding to spheres of tissue of 2 0 μm, 1 0 μm, and 0 5 μm in diameter, and for collimated 6 MV roentgen rays at 1 0 μm The results are presented in terms of event size Y, and P(Y) is the normalized probability distribution (KELLERER & ROSSI 1970)

The probability is increasing for larger event sizes as the diameter of the sphere is decreasing This means that the interactions tend to be more definitely alternative for smaller sites, i e more electrons are passing the sphere without any interaction The curve for the 6 MV roentgen rays (Fig 4) reveals that the probability is decreasing for increasing energy of the incoming gamma photons which produce more energetic electrons with lower LET values

Fig 5 illustrates the energy deposition spectra for the two radiation sources in a simulated sphere of 1 μm D(Y) = P(Y) Y is the normalized absorbed dose distribution in event sizes It illustrates the shift in energy deposition for the two sources through lower energy depositions for the 6 MV roentgen rays due to the more energetic electrons The difference in beam geometry would probably also contribute to the deposition shift, especially the influx into the counter volume of δ-electrons with higher deposition events would be of more importance in the broad beam geometry

excitation ionization potential, for water and tissue equivalent gas Z/A = 0 555 and 0 542, and I = 65 1 eV, and 62 9 eV, respectively The calculation procedure follows the method described previously (ENNOW & JESSEN 1975), but the higher cut off energies overcome the problems with the binding energies of the K-electrons.

From the slowing down spectra the relative variance in LET could be calculated and the V_{LET} values for the different radiation sources and cut off energies are listed in Table 2 For a certain energy cut off there seems to be no significant deviations in V_{LET} for the three sources The cut off energies are related to the electron ranges in tissue equivalent gas in such a way that a 5 keV electron has a range equal to the diameter of the detecting sphere at 1 μm

The values of the relative variance of the measured event distributions (also listed in Table 1) could be compared with the relative variance of the LET values V_{LET} increases for decreasing simulated volumes The total relative variance seems to be rather independent of volume but has increasing tendency for higher photon energies probably due to the straggling term

Assuming that the relative variance of the counter (KELLERER 1968) is of the order comparable to V_{track} then $V_{straggling}$ must be the dominant term in the rest of the variance and for volumes above 1 μm also more important than V_{LET} Further measurements with other geometries and detector constructions are needed to determine significant differences in the energy deposition for the two radiation qualities

Acknowledgements

The author wishes to thank Dr C B Madsen for available encouragement and support in this work and Prof T Andersen for [illegible] wishes to extend his appreciation to [illegible] of radiation physics for co-operatior [illegible] formance of the measuring chamber [illegible] work received the financial support of the Danish Medical Research Council The calculations were performed on the CDC-6400 computer at the University of Aarhus

SUMMARY

Measurements have been made on ^{60}Co gamma rays from a point so[illegible] [illegible] are performed and compared with the relative variance of the measured distributions for estimates about the straggling contri[illegible]bution

ZUSAMMENFASSUNG

Es wurden Messungen an ^{60}Co Gamma Strahlen von e[illegible] Röntgenstrahlen [illegible] vorgenommen E[illegible]

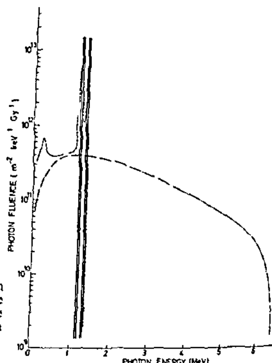


Fig 6 Three photon spectra normalized to an absorbed dose of 1 Gy (= 100 rad) in tissue equivalent gas ^{60}Co γ radiation point source (—), therapy unit (- - -) 6MV roentgen radiation (— —)

given by directly measured quantities is $V = \bar{Y}_D/\bar{Y}_F - 1$, and a corresponding relation may be given for the relative variance of the LET distribution $V_{LET} = \bar{L}_{\Delta\,D}/\bar{L}_{\Delta\,T} - 1$, where $\bar{L}_{\Delta\,D}$ is the absorbed dose average in LET and $\bar{L}_{\Delta\,T}$ is the track average in LET Δ is the cut-off energy

The relative variance of LET is calculated for three cut-off energies and for three different spectral distributions (Fig 6), measured previously (JESSEN 1973) These distributions are normalized to an absorbed dose of 1 gray (1 Gy = 100 rad, CGPM 1975) and used for calculations of the initial electrons set in motion in the tissue equivalent gas

From the primary electron spectra the slowing down spectra are calculated by means of MCGINNIES' tables (NBS 597, 1959) The table for water is applied in the calculations due to the small differences of the two parameters Z/A and I, the mean

Table 2

The relative variance in LET $V_{LET} = \bar{L}_{\Delta\,D}/\bar{L}_{\Delta\,T}$ calculated for three cut off energies and radiation sources

Δ (keV)	^{60}Co Point source	^{60}Co Therapy unit	6 MV Roentgen rays
2 5	2 39	2 36	2 55
3 6	1 73	1 72	1 80
5 1	1 21	1 21	1 23

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CLINICAL COURSE AFTER MANTLE TREATMENT OF NON-LAPAROTOMIZED PATIENTS WITH HODGKIN'S DISEASE

L BALDETORP, T LANDBERG and GUDRUN SVAHN-TAPPER

The spread of Hodgkin's disease has been the subject of several reports (SCHEER 1963, ROSENBERG & KAPLAN 1966, HAN & STUTZMAN 1967, BANFI et coll 1968, LANDBERG & LARSSON 1968, LANDBERG 1969, SMITHERS 1970, SMITHERS et coll 1974, LILLICRAP 1973)

It has usually been suggested that Hodgkin's disease often spreads along the lymphatic system in a predictable manner or that the disease arises in different sites in a more or less predictable manner In this respect, the spleen does not seem to differ from lymph nodes

Staging laparotomies, introduced by the Stanford group (1969), have greatly added to the precision in the staging of Hodgkin's disease The Stanford results (GLATSTEIN et coll 1969, KADIN et coll 1971) have largely been reproduced by other authors (JELLIFFE et coll 1970, FARRER-BROWN et coll 1971, HASS et coll 1971, PROSNITZ et coll 1972, LANDBERG et coll 1974) and indicate that in unselected patients [illegible] about 30 per cent of the patients, either [illegible]

im Diameter, die mit einem Gewebe äquivalenten Gas simuliert worden waren gemessen Es wurden Berechnungen der relativen Varians in der LET vorgenommen und mit der relativen Varians der gemessenen Verteilungen fur Abschatzungen des Streuunc Beitraes verglichen

RÉSUMÉ

Des mesures ont été faites avec un compteur proportionnel sans parois sur le rayonnement gamma ^{60}Co émis par une source ponctuelle et sur les rayons de Ronteen de 6 MV émis par un accélérateur linéaire Les spectres d'événements individuels ont été mesurés dans des régions de 0,5-2 μm de diamètre simulées avec un gaz équivalent aux tissus Les calculs de variance relative du TLE ont été faits et comparés avec la variance relative des distributions mesurées pour des évalution de la contribution du » straggling »

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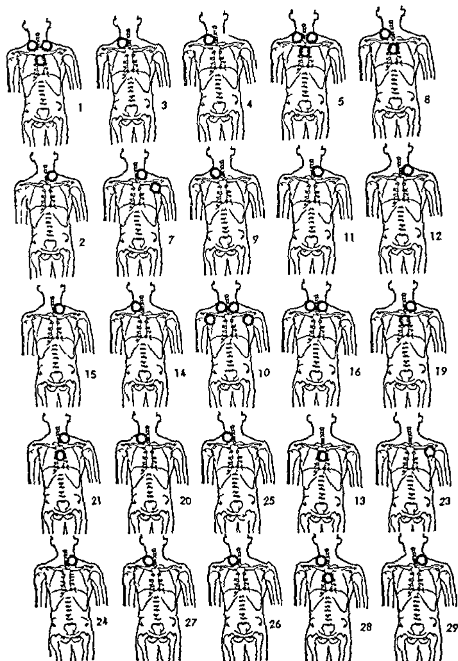
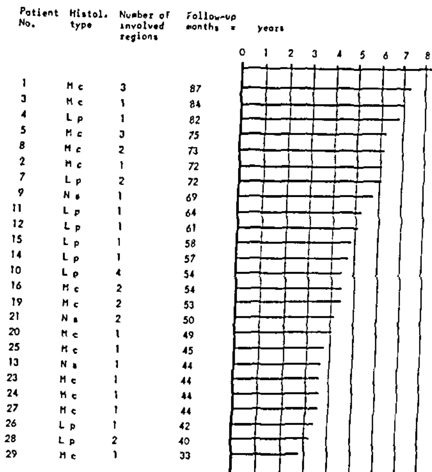


Fig 2. Manifestations in 25 pat ents be ng alive and continuously symptom-free after mantle treat ment for suprad aphragmatic Hodgkin s disease O = involved lymph node region.



Patient No.	Histol. type	Number of involved regions	Follow-up months = years
1	M c	3	87
3	M c	1	84
4	L p	1	82
5	M c	3	75
8	M c	2	73
2	M c	1	72
7	L p	2	72
9	N s	1	69
11	L p	1	64
12	L p	1	61
15	L p	1	58
14	L p	1	57
10	L p	4	54
16	M c	2	54
19	M c	2	53
21	N s	2	50
20	M c	1	49
25	M c	1	45
13	N s	1	44
23	M c	1	44
24	M c	1	44
27	M c	1	44
26	L p	1	42
28	L p	2	40
29	M c	1	33

Fig 1 Twenty five patients being alive and without evidence of disease after mantle treatment for supradiaphragmatic Hodgkin's disease L p = Lymphocyte predominance M c = Mixed cellularity N s = Nodular sclerosing type

upwards or downwards Even higher figures were reported by the British Lymphoma Investigation (1975) in which it was found that in early Hodgkin's disease, intra abdominal involvement was found in 47 per cent of patients, where other diagnostic methods, including lymphography, had not revealed disease below the diaphragm

It is today not clear whether the more proper staging through laparotomy offers a better prognosis for the patient, even if this on general oncologic grounds would seem most likely The complications of surgery and any harmful effect of removal of the spleen must be considered

The spread of Hodgkin's disease in patients considered to have supradiaphragmatic disease is now reported Mantle treatment was given without preceding staging laparotomy Previously, a preliminary report has been presented (LANDBERG 1974)

Material and Methods The series includes 42 patients, 24 males and 18 females with supradiaphragmatic Hodgkin's disease, admitted 1967–1971 Thus, they all

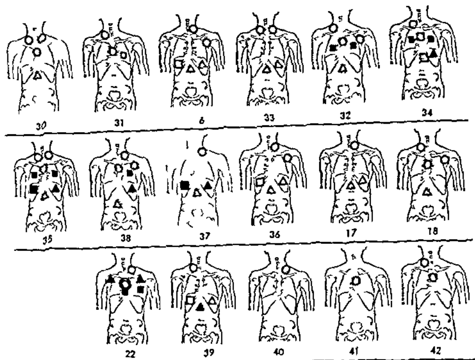
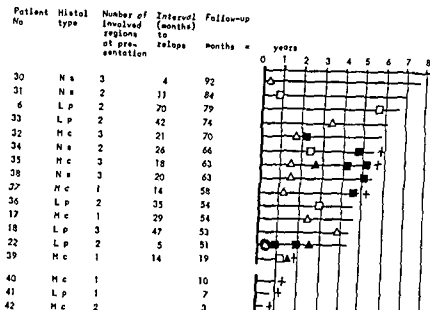


Fig 4 Seventeen patients who had either relapsed or were dead at the end of follow up after mantle treatment for supradiaphragmatic Hodgkin s disease O involved lymph node regions at beginning of treatment, △ = first relapse occurring in lymph nodes or spleen □ = first relapse occurring in other tissues ▲ ■ = later manifestations, ◎ = local recurrence being first relapse

Results and Discussion

Twenty five patients, 15 males and 10 females, are alive without evidence of disease after the primary treatment (Figs 1, 2) The age of these patients ranged between 6 and 67 years with a median of 24 and a mean of 30 (SD 17) The follow-up for these patients ranged between 33 and 87 months with a median of 54 and a mean of 58 (SD 15) Nine patients had lymphocyte predominance, 13 had mixed cellularity and 3 had nodular sclerosing Hodgkin's disease In 16 (Fig. 2), only one lymph node region was involved, 6 had 2 regions and 3 patients 3 or 4 regions involved All but 2 had cervical lymphadenopathy, as sole involvement in 15 (in 8 patients on the right side in 6 on the left and in one bilaterally) Seven patients had mediastinal involvement in one as the only finding

Seventeen patients 9 males and 8 females, had either relapsed or died without evidence of disease after the primary treatment (Figs 3, 4) The age of the patients ranged between 16 and 64 years with a median of 26 and a mean of 32 years (SD 15) The follow up for these patients ranged between 3 and 92 months with a median of 58 and a mean of 53 months (SD 27) Six had lymphocyte predominance, 7 had mixed



Patient No	Histol type	Number of involved regions at presentation	Interval (months) to relapse	Follow-up months
30	N s	3	4	92
31	N s	2	11	84
6	L p	2	70	79
33	L p	2	42	74
32	M c	3	21	70
34	N s	2	26	66
35	M c	3	18	63
38	N s	3	20	63
37	M c	1	14	58
36	L p	2	35	54
17	M c	1	29	54
18	L p	3	47	53
22	L p	2	5	51
39	M c	1	14	19
40	M c	1		10
41	L p	1		7
42	M c	2		3

Fig 3 Seventeen patie[illegible] mantle treatment for [illegible] M c = Mixed cellularity [illegible] or spleen, □ = first relapse occurring in other tissues, ▲■ = later manifestations O = local recurrence, † = dead

have a possible follow-up of at least 3 years, which was chosen since it has been stated (SPITTLE et coll 1973) that 90 per cent of relapses in Hodgkin's disease appear within 3 years

The age of the patients ranged between 6 and 67 years with a median age of 26 and a mean of 31 (SD 17)

None of the patients had a staging laparotomy before treatment In all cases the disease was considered to be confined to supradiaphragmatic lymph nodes Lymphography was performed before treatment in 33 patients In a later series, consisting of 32 patients subjected to staging laparotomy, the agreement between lymphographic evaluation and histology was 94 per cent (LANDBERG et coll 1974) Scintigraphy of the liver and spleen was performed in 40 of the patients In the 32 laparotomized patients, all 11 with involvement of the spleen at histology had a positive scintigraphy Fifteen of the patients had lymphocyte predominance, 20 had mixed cellularity, and 7 had the nodular sclerosing type of Hodgkin's disease Only 2 had definite systemic symptoms

All patients were treated with mantle technique (SVAHN-TAPPER 1970, SVAHN TAPPER & LANDBERG 1971) Usually the irradiation was administered in two series up to an absorbed dose in the target of 40 Gy (4 000 rad) in 27 fractions over 10 weeks This technique has proved to give a local recurrence in only 3 per cent of the patients (SVAHN-TAPPER et coll, to be published)

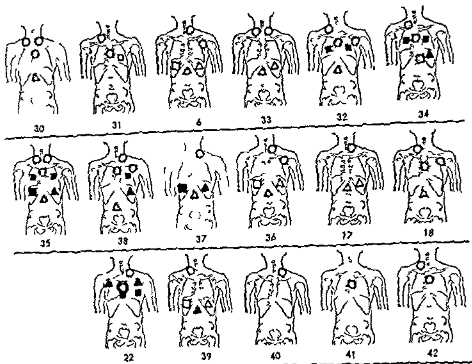


Fig 4 *Seventeen patients* who had either relapsed or were dead at the end of follo... after mantle treatmen... fo ... ...gions at ... lapse occ...

Results and Discussion

Twenty five patients, 15 males and 10 females, are alive without evidence of disease after the primary treatment (*Figs* 1, 2) The age of these patients ranged between 6 and 67 years with a *median* of 24 and a mean of 30 (SD 17) The follow-up for these patients ranged between 33 and 87 months with a median of 54 and a mean of 58 (SD 15) Nine patients had lymphocyte predominance, 13 had mixed cellularity and 3 had nodular sclerosing Hodgkin's disease In 16 (Fig 2), only one lymph node region was involved, 6 had 2 regions and 3 patients 3 or 4 regions involved All but 2 had cervical lymphadenopathy, as sole involvement in 15 (in 8 patients on the right side in 6 on the left and in one bilaterally) Seven patients had mediastinal involvement, in one as the only finding

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Table

Interval between beginning of mantle treatment and relapse in 14 patients

Months after beginning of mantle treatment	Accumulated number of patients with relapse
4	1
5	2
11	3
14	5
18	6
20	7
21	8
26	9
29	10
35	11
42	12
47	13
70	14

cellularity and 4 had nodular sclerosing Hodgkin's disease In 5 patients (Fig 4) only one lymph node region was involved at the beginning of the treatment, in 7 patients 2 regions and in 5 patients 3 regions were involved All but one had cervical lymphadenopathy (on the right side in 6, on the left in 7, and bilaterally in 3) Nine patients had mediastinal lymphadenopathy

The time interval between the beginning of the mantle treatment and relapse as well as localization of relapses appear in Figs 3 and 4 Three patients (Nos 40, 41, 42) have died without evidence of relapsing disease The exact cause of death in these patients is not known, since they died at other hospitals and only incomplete data are available

One patient (No 22) had a local (true) recurrence, whereas the new manifestation of disease in the remaining 13 patients represented extension The interval between the beginning of mantle treatment and relapse (Table) ranged between 4 and 70 months with a median of 21 and a mean of 25 (SD 18) There does not seem to be any particular time clustering for relapse Ten of the patients with relapse are still alive after 51 to 92 months (median 59, mean 67), whereas 4 have died after 19 to 66 months (median 61, mean 52)

In 11 patients the first relapse included abdominal lymph nodes, and in addition the spleen was involved in 2 and the liver and the spleen in 2 One patient had a relapse in the liver and spleen, one had an extension to the lung tissue, and one had a local recurrence Seven of the 14 patients with relapse have later had further extension

Thus, of totally 39 patients with clinically supradiaphragmatic Hodgkin's disease,

staged without laparotomy, 12 (31 per cent) have later relapsed in abdominal sites Four of the relapses occurred after more than 3 years, namely after 35, 42, 47, and 70 months, respectively The figure 31 per cent may therefore represent a minimum, since some of the patients being free of signs of disease may actually still be at risk for a relapse This figure may then be considered to agree reasonably well with the figures given in the literature on the frequency of abdominal involvement, discovered at laparotomy It might then indicate that occult abdominal disease at least in a substantial number of patients sooner or later will give symptoms

The small number of cases in the present series does not allow for statistical significance However, no difference between patients without and those with relapse was found regarding the distribution on sex, age and histologic types, whereas patients without relapse more often had only one lymph node region involved than those with relapse

SUMMARY

Forty two patients with Hodgkin s disease were staged without laparotomy and considered to have only supradiaphragmatic disease They were treated with the mantle technique and followed up for at least 3 years Abdominal extension was later found in 31 per cent It is concluded that occult abdominal disease usually in course of time will give symptoms

ZUSAMMENFASSUNG

42 Patienten mit Hodgkinscher Erkrankung, die ohne Laparatomie Stad

abdominale Erkrankung im Laufe der Zeit gewöhnlich zu Symptomen führt

RÉSUMÉ

Le stade de la maladie de Hodgkin a été
ces malades ont été considérés comme
Ils ont été traités par la technique en m
ultérieurement une extension abdomi chez 31 pour cent de ces malades Les auteurs en concluent que l'atteinte abdominale occulte se révèlera ultérieurement

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HYPOPHARYNGEAL CARCINOMA

Long-term survivors following radical radiation therapy

T INOUE and Y SHIGEMATSU

Most of the patients with carcinoma of the hypopharynx are already in an advanced stage when first seen, because of the highly malignant nature of the disease and of the long interval between the onset of symptoms and the diagnosis The results of treatment of hypopharyngeal carcinoma reported vary widely, depending on the material and the method of treatment, with the 5-year survival rate ranging from 5 to 60 per cent Although head and neck surgeons report 5 year survival rates of 20-25 per cent in the operable cases, plastic surgery is often required following the initial laryngo-pharyngectomy, an extremely arduous procedure for the patient Furthermore, patients not uncommonly develop local recurrences or distant metastases soon after, or even during the course of plastic surgery For these reasons, radiation therapy has been widely adopted for radical treatment as well as an adjuvant for surgery

The policy for treating carcinoma of the hypopharynx at this hospital has been discussed previously (INOUE et coll 1973) The aim of this report is to evaluate the cases successfully treated by radiation

Material and Methods

Between January 1961 and June 1971, 167 histologically proven squamous cell carcinomas of the hypopharynx were treated, in 88 cases (85 males and 3 females) the piriform sinus was involved, in 44 (2 males and 42 females) the postcricoid region,

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HYPOPHARYNGEAL CARCINOMA

Long-term survivors following radical radiation therapy

T INOUE and Y SHIGEMATSU

Most of the patients with carcinoma of the hypopharynx are already in an advanced stage when first seen, because of the highly malignant nature of the disease and of the long interval between the onset of symptoms and the diagnosis The results of treatment of hypopharyngeal carcinoma reported vary widely, depending on the material and the method of treatment, with the 5-year survival rate ranging from 5 to 60 per cent Although head and neck surgeons report 5-year survival rates of 20–25 per cent in the operable cases, plastic surgery is often required following the initial laryngo-pharyngectomy, an extremely arduous procedure for the patient Furthermore patients not uncommonly develop local recurrences or distant metastases soon after, or even during the course of plastic surgery For these reasons, radiation therapy has been widely adopted for radical treatment as well as an adjuvant for surgery

The policy for treating carcinoma of the hypopharynx at this hospital has been discussed previously (INOUE *et coll* 1973) The aim of this report is to evaluate the cases successfully treated by radiation

Material and Methods

Between January 1961 and June 1971, 167 histologically proven squamous cell carcinomas of the hypopharynx were treated, in 88 cases (85 males and 3 females) the piriform sinus was involved, in 44 (2 males and 42 females) the postcricoid region,

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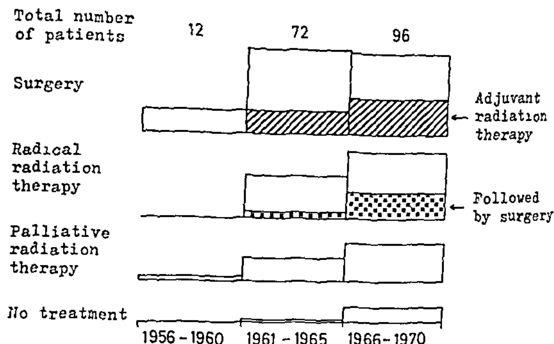


Fig 1 One hundred and eighty patients with carcinoma of the hypopharynx divided into 3 periods between 1956 and 1970 Before 1960, no patients were treated by radical radiation therapy

and in 35 cases (23 males and 12 females) the posterior pharyngeal wall Of these, only 15 cases were found in stages T1 and T2, and the other 152 cases were graded as T3

	N0	N1	N2	N3	M1
T1	8	3	—	1	—
T2	2	—	—	1	—
T3	63	34	3	50	2*

2* T3N3M1

Ninety-four cases (56 %) had metastases in lymph nodes in the neck at registration

Before 1960, no patients with hypopharyngeal carcinoma were treated by radical irradiation at this hospital With the increasing contact between surgeons and the radiation therapists and with the improvement of the equipment from orthovoltage to supervoltage range, the number of patients allocated to curative doses of radiation therapy has steadily increased in number (Fig 1)

Of the total cases under consideration, nearly half (81) were treated initially with surgery and the remainder (86) primarily with irradiation Sixteen of 55 cases treated with radical irradiation later were operated upon for local recurrences (Table 1) Of the 8 early cases of T1N0, 6 were given radical radiation therapy, one was treated with surgery alone, and the other one was treated by surgery after preoperative radiation therapy

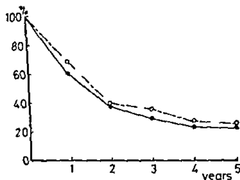


Fig. 2. Results of carcinoma of the hypopharynx treated between January 1961 and June 1971 and followed to June 30th, 1974

Radical radiation therapy was more frequently administered to patients with carcinoma of the posterior pharyngeal wall (9 males and 7 females), than to those with lesions at other sites (postcricoid region 11 females, and piriform sinus 27 males and 1 female) The TNM-classification was as follows

	N0	N1	N2	N3
T1	6	—	—	—
T2	—	—	—	1
T3	26	4	1	17

Results

The 1-, 3 , and 5-year cumulative survival rates of the patients with radical radiation therapy were 69, 36 and 25 per cent, respectively The overall survival rates were 61 29 and 22 per cent, respectively (Fig 2)

Previously (INOUE et coll), it was reported that 80 per cent of local recurrences or distant metastases developed within 18 months after initial irradiation Although

Table 1

Method of treatment

Treatment	No of patients
Surgery alone	52
Preoperative irradiation	25
Postoperative irradiation	4
Radical irradiation	39
Radical irradiation followed by surgery	16
Palliative irradiation	31

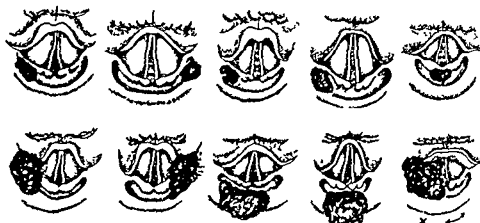


Fig 3 Laryngoscopy of 10 patients who were treated by radical radiation therapy alone and survived more than 3 years without recurrence

some recurrences may have occurred on further follow-up, the results may be evaluated after an observation period of 3 years The 3 year survivors (Table 2) after radical radiation therapy alone were 4 patients with T1N0 carcinoma of the piriform sinus, one with T1N0 of the postcricoid, 3 with T3N0 of the posterior pharyngeal wall, one with T3N3 of the piriform sinus and one with T3N3 of the posterior pharyngeal wall These results indicate that carcinomas of the posterior pharyngeal wall can be controlled by radiation therapy even with advanced lesions, while in other types of this disease radiation therapy was only successful in the early cases

Surgery is the only curative treatment for cases with local recurrence after radical radiation therapy Although it has been said that surgery in such heavily irradiated cases is accompanied by severe complications, 8 patients in this material were operated upon successfully with minimal complications

The localisation and grade of cases treated by irradiation alone, controlled at 3 years, appear in Fig 3 In 8 of the 10 cases the lesion was found at the upper part of the hypopharynx and was of exophytic appearance

Table 2

Three year results of hypopharyngeal carcinoma treated by radical irradiation

	Piriform sinus	Postcricoid	Posterior pharyngeal wall
T1N0	4/4	1/1	*1/1
T2N3	—	—	0/1
T3N0	***3/11	**2/7	*4/8
T3N1	0/1	0/1	0/2
T3N2	—	—	—
T3N3	*2/12	0/2	1/3

Number of patients (1* 2** or 3***) later cured by surgery



Fig 4 Case 1 a) Exophytic tumor of the left lateral wall of the piriform sinus no extension into the lower part of the sinus b) 4 months after treatment

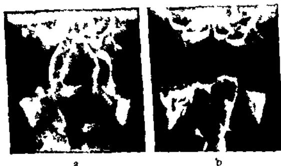


Fig 5 Case 2 a) Round tumor of the right posterior pharyngeal wall, extension to the right aryepiglottic and pharyngoepiglottic folds b) One month after treatment

Case reports

Case 1 (Fig 4) A 52 year-old man was admitted with a squamous cell carcinoma of the hypopharynx Laryngography showed an exophytic tumor of the left upper lateral wall of the piriform sinus without extension to the lower part (Fig 4 a) No cervical lymph node was palpable (T1N0) Treatment with tele-cobalt began 3 days later; a tumor dose of 44 Gy (4 400 rad) was given in 5 weeks with parallel opposing portals of 10 cm × 15 cm encompassing the whole neck followed by an additional dose of 36 Gy (3 600 rad) delivered with reduced portals of 6 cm 8 cm The patient received a total dose of 80 Gy (8 000 rad) in 40 fractions over 58 days At laryngography 4 months after the completion of radiation therapy no evidence of tumor was found (Fig 4 b) Two months thereafter, the patient developed a perichondritis which was treated by steroid medication over 6 months and underwent an emergency tracheostomy About a year later the tracheostoma was closed The patient has done well since that time and there was no evidence of tumor 8 years after the beginning of treatment

Case 2 (Fig 5) A 68 year old man was admitted with a squamous cell carcinoma of the hypopharynx Laryngography showed a round tumor on the right posterior pharyngeal wall with extension to the right aryepiglottic and pharyngoepiglottic folds (Fig 5 a) No lymph node was palpable in the neck (T3N0) Using a tele-cesium unit a total tumor dose of

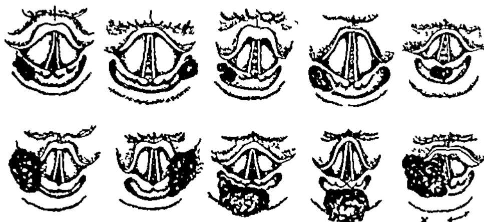


Fig 3 Laryngoscopy of 10 patients who were treated by radical radiation therapy alone and survived more than 3 years without recurrence

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Surgery is the only curative treatment for cases with local recurrence after radical radiation therapy Although it has been said that surgery in such heavily irradiated cases is accompanied by severe complications, 8 patients in this material were operated upon successfully with minimal complications

The localisation and grade of cases treated by irradiation alone, controlled at 3 years, appear in Fig 3 In 8 of the 10 cases the lesion was found at the upper part of the hypopharynx and was of exophytic appearance

Table 2

Three year results of hypopharyngeal carcinoma treated by radical irradiation

	Piriform sinus	Postericoid	Posterior pharyngeal wall
T1N0	4/4	1/1	*1/1
T2N3	—	—	0/1
T3N0	***3/11	**2/7	*4/8
T3N1	0/1	0/1	0 2
T3N2	—	—	—
T3N3	*2/12	0/2	1/3

Number of patients (1* 2** or 3***) later cured by surgery



Fig 4 Case 1 a) Exophytic tumor of the left lateral wall of the piriform sinus, no extension into the lower part of the sinus b) 4 months after treatment

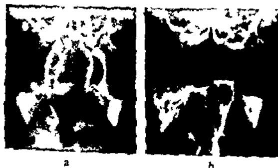


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Case 2 (Fig 5) A 68-year-old man was admitted with a squamous cell carcinoma of the hypopharynx Laryngography showed a round tumor on the right posterior pharyngeal wall with extension to the right aryepiglottic and pharyngoepiglottic folds (Fig 5 a) No lymph node was palpable in the neck (T3N0) Using a tele-cesium unit, a total tumor dose of



Fig 6 Case 3 a) Huge tumor of the posterior pharyngeal wall extension to the posterior oropharyngeal wall b) 2 years after treatment

52 Gy (5 200 rad) was delivered in 26 fractions over 30 days with parallel opposing portals of 6 cm 7 cm One month after the treatment laryngography showed no remaining tumor (Fig 5 b) There was no evidence of tumor 10 years later

Case 3 (Fig 6) A 64 year old man was referred with a squamous cell carcinoma of the hypopharynx Laryngography revealed a bulky tumor of the posterior pharyngeal wall extending to the posterior oropharyngeal wall without invasion of the lower part (Fig 6 a) There was a fixed jugulo digastric lymph node of 2 cm × 2 5 cm and a movable homolateral posterior cervical node 1 5 cm in diameter (T3N3) Telecobalt therapy with a tumor dose of 56 Gy (5 600 rad) was given in 5 1/2 weeks with parallel opposing portals of 8 cm 14 cm and then an additional dose of 20 Gy (2 000 rad) was given in 2 weeks with reduced portals of 6 cm × 10 cm *In total the patient received a tumor dose of 76 Gy (7 600 rad) in 36 frac* tions over 53 days Two years after the treatment laryngography showed no tumor (Fig 6 b) The patient died of respiratory disease after 3½ years No autopsy was performed but the patient was without clinical evidence of recurrence or distant metastases up to his death

Discussion

It seems difficult to indicate one particular procedure for the treatment of patients with hypopharyngeal carcinoma taking account of the great variety of the disease by site and stage

Since this *disease is usually encountered in an advanced stage with a highly malig* nant nature differing markedly from laryngeal carcinoma (SATO 1972 JORGENSEN 1971) treatment with irradiation and surgery combined has been widely used Post operative radiation therapy was recommended by LEROUX ROBERT (1956) and MACCOMB & FLETCHER (1967) and preoperative radiation therapy seems to have been used more commonly recently OGURA & BILLER (1970) advocated a planned low dose preoperatively whereas FREDRICKSON & STRAHAN (1969) recommended a semicurative preoperative radiation therapy In the previous report (INOUE et coll)

irradiation therapy was recommended for the first step of the treatment, on the assumption that the final choice between irradiation and surgery would be made during the course of irradiation therapy

In spite of the trend for surgeons to use irradiation as an adjuvant treatment, it is obvious that the cases controlled by this therapy alone have the most useful life because of the preserved laryngopharyngeal function Since the proportion of patients cured by radiation therapy has not been satisfactorily high, it seems important to analyse the cases in detail in which radical radiation therapy was successful

For early exophytic carcinoma, radical radiation therapy was recommended by MacComb & Fletcher and Lalanne et coll (1971) Leroux-Robert, Smith et coll (1963), Wang (1971), and Lord et coll (1973) reported that carcinoma of the posterior pharyngeal wall without nodal disease could also be controlled by radiation therapy even in an advanced lesion

Concerning carcinoma of the postcricoid region, Garrett (1971) reported four 5-year survivors out of 24 patients irradiated using double wedge technique Umegaki (1972) also reported that 3 of 9 far advanced patients (T3N3) treated with irradiation survived for more than 4 years In spite of these results, in our experience postcricoid carcinomas have been difficult to control by radiation therapy

Carcinomas of the upper part of the hypopharynx seem more curable by irradiation than those of the lower part Baclesse (1949) suggested that more fungating tumors occur in the upper part, while more flat and ulcerating tumors occur in the lower part, and the latter tend to infiltrate more widely In the present material, in 8 of 10 patients controlled by radiation therapy for more than 3 years, the tumor was found at the upper part of the hypopharynx Since hypopharyngeal carcinomas can only be partially examined by indirect laryngoscopy, laryngography and oesophagus examination should not be omitted, as these radiologic procedures are useful in defining the inferior margin of the tumor

SUMMARY

In a material of 167 cases with squamous cell carcinoma of the hypopharynx, treated between 1961 and 1971, radical irradiation was administered to 55 patients Of these latter patients the 3- and 5-year survival rates were 36 and 25 per cent, respectively The lesions of the upper part of the hypopharynx were found to be more curable than those of the lower part Three cases are presented in detail

ZUSAMMENFASSUNG

Bei einem Material von 167 Fallen mit einem Schuppenzellkar[illegible] [illegible] oberen Teils des Hypopharynx waren besser heilbar als die des unteren Teils Es werden drei Fälle im Einzelnen vorgestellt

RÉSUMÉ

Sur une série de 167 cas de carcinome épidermoïde de l hypopharynx traités entre 1961 et 1971, 55 malades ont eu une irradiation radicale Parmi ceux-ci, les taux de survie à 3 et 5 ans ont éte respectivement de 36 et 25 pour cent Les lésions de la partie supérieure de l hypopharynx se sont révélées plus curables que celles de la partie inferieure Trois cas sont presentees en detail

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MALIGNANT NASOPHARYNGEAL TUMOURS

Result of radiation therapy

LARS GUNNAR LARSSON and IRENE SEELIG

During the ten year period 1959 to 1968 a total number of 61 patients with malignant nasopharyngeal tumours were admitted to the radiation therapy department in Umeå. The department received its patients from the three most northern counties in Sweden (Västernorrland, Västerbotten and Norrbotten), a vast area extending from 62° to 69° latitude, which during these years had an average population of 0.78 millions. As the only radiation therapy center within this region, the department probably received all, or almost all, new cases diagnosed. During the same period a total of 520 new cases were registered in the whole of Sweden (Swedish Cancer Register), which gives an annual incidence of 0.68 per 100 000, while the Umeå series corresponds to an annual incidence of 0.78 per 100 000. The male/female ratio was in the Umeå series 1.45 and in the whole of Sweden 1.56, the age distribution was similar in the Umeå series and in the registered cases from the whole of Sweden (Fig. 1).

Clinical features. Nasopharyngeal malignant tumours are from many points of view strange tumours. Despite their usually highly malignant microscopic appearance, some patients present a remarkably long history. Despite advanced local and regional disease most patients are on admission in good general condition, and metastases outside the neck are at this time rarely found. Some patients may live several years

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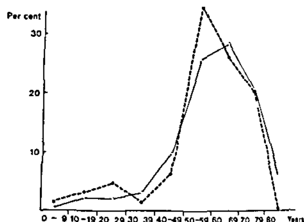


Fig 1 Age distribution of malignant *nasopharyngeal tumours in the whole* of Sweden (Cancer Register, continuous line) and in the Umeå series (broken line)

with uncontrolled or recurrent disease and it is not rare that recurrences or metastases appear a long time after treatment This means that the nasopharyngeal carcinoma is a tumour, biologically rather different from most epidermoid carcinomas in the upper respiratory and digestive tracts This is of special interest in view of the immuno logic and virologic findings about this tumour during recent years (HENLE et coll 1970, DE SCHRYVER et coll 1971, 1974)

In the present series 28 patients had a history of 6 months or more on admission (Table 1), and 20 of these patients had anaplastic or poorly differentiated carcinoma Among the cases with a long history (more than one year) 10 out of 12 had this type of tumour As in all reported series most patients had relatively advanced disease, 42 patients (69 per cent) had neck node metastases and only 7 patients had really early disease (tumour limited to nasopharynx and no neck node metastases) Nevertheless the general condition was recorded as good in all but two patients and no patient in this series had evidence of metastases outside the neck on admission

After treatment 6 patients had a remarkably long survival (6 to 10 years) despite remaining or recurrent disease Five of these patients had poorly differentiated carcinoma and one had *reticulum cell sarcoma Most remarkable was a man*, aged 28, with poorly differentiated carcinoma and unilateral neck node metastases who

Table 1

Duration of history

Time (months)	No of cases
24	4
12–23	8
6–11	18
3–5	17
1 2	12
1	2

Table 2

Pathology and survival

Pathology	Survival			
	Symptom free		Crude	
	3 years	5 years	3 years	5 years
Poorly differentiated carcinoma	17/42	12/42	29 42	16 42
Differentiated squamous cell carcinoma	2/8	2/8	3/8	3/8
Reticulum cell sarcoma	4/6	4 6	4/6	4 6
Unclassified	1/2	1/2	1/2	1/2
Plasmocytoma	2/2	2/2	2/2	2/2
Adenocarcinoma (acinic cell carcinoma)	0/1	0 1	0/1	0/1
Total	26/61 (42 %)	21/61 (34 %)	30 61 (49 %)	26 61 (43 %)

lived without signs of disease in 9 years, then mediastinal, pulmonary and pleural metastases developed

Classification Most pathologists now agree that the majority of the malignant nasopharyngeal tumours represent anaplastic or poorly differentiated carcinoma probably of squamous cell origin (YEH 1962, BAUER & MCGAVRAN 1968) Many of these tumours were previously classified as lymphoepithelioma transitional cell carcinoma or even malignant lymphoma Differentiated squamous cell carcinoma and reticulum cell sarcoma (histiocytic and stem cell lymphoma) constitute two important minority groups while all the other tumour types are very rare (plasmocytoma, salivary gland type adenocarcinoma and mesenchymal sarcoma)

In the present series all specimens were examined in the same pathology department and they were continuously discussed with the pathologists concerning the classification The distribution between the different microscopic types appears in Table 2 The two cases recorded as unclassified both probably represented anaplastic carcinoma or reticulum cell sarcoma, but the material was insufficient for definite classification

No good generally accepted system for the clinical classification exists at present The UICC classification is not suitable for a retrospective analysis A distinction between T1 and T2 cases is difficult and it seems unnatural to separate homolateral and contralateral involvement of the neck nodes when the primary tumour is located in a mid line structure like nasopharynx Therefore, the simplified classification presented in Table 3 was used The neck node metastases were in almost all cases microscopically confirmed, usually by fine-needle aspiration biopsy and cytology In the few cases where microscopy of the neck node metastases was not performed, the secondaries were clinically obvious

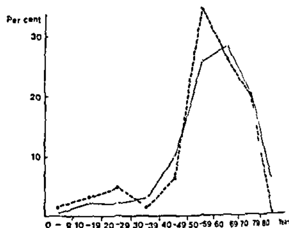


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1 2	12
1	2

Table 4

Five year result of radiation therapy of the 61 patients

Number of cases		
Living symptomfree	21 (34 %)	(43 %)
Living, with tumour	5	
Dead, with tumour	30	
Dead, intercurrent disease, no signs of malignancy	5	

was irradiated with 200 kV (0 5 mm Cu filter, 60 to 70 cm distance) using two semitangential, alternating beam directions and with a total dose of 3 300 to 3 600 R in 2 to 3 weeks In cases with bilateral neck node metastases also the other side of the neck was treated in the same way but not until 2 months later when the reaction after the first treatment series had subsided

In all the other cases the primary tumour was treated with ^{60}Co-kilocurie beam or, in most cases, with 31 MV roentgen radiation from a betatron usually from two opposing ports and with daily treatments 5 days per week The tumour dose was in most cases 5 000 to 6 500 rad in 30 to 45 days Neck node metastases were treated in a similar way, with the only difference that the 200 kV dose was limited to about 3 000 R and followed by supplementary ^{60}Co-kilocurie treatment with a total of 600 to 1 200 rad given with daily fractions in 3 to 4 days This supplementary treatment was limited to a smaller field including the palpable neck node metastases (usually upper part of the neck) The treatment technique is schematically illustrated in Fig 2

Prophylactic neck node irradiation was, with few exceptions, not given in this series and a neck side was as a rule irradiated only if there were microscopically confirmed or clinically obvious metastases

Results

The overall 5-year results are listed in Table 4 The crude 5-year survival was 43 per cent and the tumour-free 5-year survival 34 per cent If the cases of plasmocytoma and salivary gland type adenocarcinoma were excluded, the corresponding figures were 41 and 33 per cent Table 2 illustrates the survival in the different microscopic groups All groups with the exception of the poorly differentiated carcinomas are too small to allow any comparison with other series It may be noted, however, that the reticulum cell sarcomas had a better prognosis than the carcinomas and that the two plasmocytomas remained symptom-free after treatment The 10-year crude survival rate was about 20 per cent (Table 5)

As could be expected, a close correlation existed between the anatomic extension of the disease and the prognosis, both if the extension of the primary tumour and that of the neck node metastases were analysed separately, or if these factors were com-

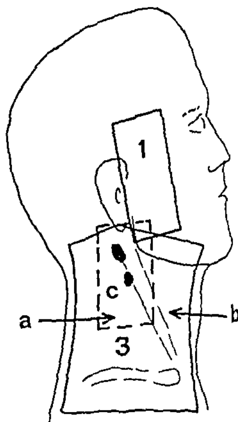


Fig 2 Schematic illustration of the most frequent treatment technique The primary tumour was treated with 2 opposing 31 MV beams (fields 1 and 2) up to a tumour dose of 5 000 to 6 500 rad in 30 to 45 days with 5 fractions per week An involved neck node region was treated with 200 kV using two alternating, semitangential beam directions (fields 3 a and 3 b) Usually 300 R per day during 5 days per week were given up to a total dose of about 3 000 R This was followed by a booster dose of 600 to 1 200 rad with ^{60}Co beam to the palpable lymph node metastases (field 3 c) divided in 3 to 4 fractions and given during consecutive days from the same side of the neck

Treatment Up to July 1962 (17 cases) the primary tumour was irradiated with 200 kV (0 5 mm Cu filter, 50 cm distance) roentgen radiation from two lateral and two medial anterior fields with lead protection for the eyes Each field usually received about 3 000 R and the whole treatment period was 4 to 5 weeks with 5 treatments per week If the patient had unilateral neck node metastases this side of the neck

Table 3

Clinical staging

Primary tumour

- P_1 limited to nasopharynx
- P_2 extending outside nasopharynx without erosion of base of skull
- P_3 erosion of base of skull

Cervical lymph nodes

- L_0 no metastases
- L_1 unilateral metastases
- L_2 bilateral metastases

Stage

- A P_1L_0
- B P_1L_1 P_2L_0
- C P_2L_1, all P_3 and L_2

Table 8

Five year survival

	Crude	Symptom free
Stage A	6/7 (85%)	5/7 (72%)
Stage B	14/25 (54%)	11/25 (44%)
Stage C	4/26 (15%)	3/26 (12%)
Total	24/58 (41%)	19/58 (33%)

Table 9

Primary irradiation of the neck

Bilateral neck irradiation	
Bilateral therapeutic	14
Unilateral therapeutic + unilateral prophylactic	1
Bilateral prophylactic	3
Unilateral neck irradiation	
Therapeutic	27
Prophylactic	3
No neck irradiation	10
Total	58

In 40 cases one side or both sides of the neck were not irradiated

Surgical neck dissection played only a minor role in the treatment of these patients, as in most other published materials In 5 of the patients unilateral neck dissection was performed due to remaining or recurring nodes after irradiation (4 cases), or appearances of lymph node metastases in a previously unirradiated neck side (one case) Three of these patients died from their tumour within 5 years after the dissection one died from intercurrent disease after 9 months without signs of tumour and one patient is still alive without symptoms or signs of tumour 6 years after dissection

Some authors have stressed the importance of prophylactic irradiation of the neck lymph node regions (CHEN & FLETCHER 1971, LEDERMAN 1961) while other authors have limited treatment to clinically involved neck sides (Radiumhemmet, method quoted by DE SCHRYVER 1971, BERTELSEN et coll 1975) In the present series prophylactic irradiation to one or both sides of the neck was given in only 7 cases (Table 9) In a total of 40 patients one or both sides of the neck were primarily unirradiated (Table 9) A retrospective analysis of these cases made it highly unlikely that prophylactic irradiation could have added significantly to the cure rate, and only one patient was found where such treatment theoretically could have been curative (Table 10) Some of the 17 patients listed in the table, who got local recurrences of the disease had also neck node metastases in previously unirradiated volume, prophylactic treatment could in these cases have modified the course of the disease, but not cured the patients

Table 5

Ten year crude survival

Years	No. of cases	Per cent
1	50/61	83
2	39/61	64
3	30/61	49
4	28/61	46
5	26/61	43
6	22/61	36
7	21/61	35
8	15/52	29
9	11/47	24
10	9/42	21

bined in a staging (Tables 6 to 8, the cases of plasmocytoma and salivary gland type adenocarcinoma are excluded). It is evident that most cures or long term survivors in the present series had relatively early disease, while the patients with advanced disease, as destruction of the base of the skull or bilateral neck node metastases had in general poor prognosis. No significant difference in prognosis was found between the series treated with only 200 kV roentgen rays and the cases treated with supervoltage irradiation. These two series were, however, too small for any definite comparison.

Table 6

Five year crude survival

	L_0	L_1	L_2	Total
P_1	6/7	10/19	2/9	18/35 (51 %)
P_2	4/6	0/4	0/2	4/12 (33 %)
P_3	0/3	2/5	0/3	2/11 (18 %)
Total	10/16 (62 %)	12/28 (43 %)	2/14 (14 %)	24/58 (41 %)

Table 7

Five year symptom free survival

	L_0	L_1	L_2	Total
P_1	5/7	7/19	2/9	14/35 (40 %)
P_2	4/6	0/4	0/2	4/12 (33 %)
P_3	0/3	1/5	0/3	1/11 (9 %)
Total	9/16 (56 %)	8/28 (29 %)	2/14 (14 %)	19/58 (33 %)

Table 8

Five year survival

	Crude		Symptom free	
Stage A	6/7	(85 %)	5/7	(72 %)
Stage B	14/25	(54 %)	11/25	(44 %)
Stage C	4/26	(15 %)	3/26	(12 %)
Total	24/58	(41 %)	19/58	(33 %)

Table 9

Primary irradiation of the neck	
Bilateral neck irradiation	
Bilateral therapeutic	14
Unilateral therapeutic + unilateral prophylactic	1
Bilateral prophylactic	3
Unilateral neck irradiation	
Therapeutic	27
Prophylactic	3
No neck irradiation	10
Total	58

In 40 cases one side or both sides of the neck were not irradiated

Surgical neck dissection played only a minor role in the treatment of these patients, as in most other published materials. In 5 of the patients unilateral neck dissection was performed due to remaining or recurring nodes after irradiation (4 cases), or appearances of lymph node metastases in a previously unirradiated neck side (one case). Three of these patients died from their tumour within 5 years after the dissection, one died from intercurrent disease after 9 months without signs of tumour and one patient is still alive without symptoms or signs of tumour 6 years after dissection.

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Table 10

Course of disease in 40 cases in which one side or both sides of the neck were not primarily irradiated	
Living free from disease 5 years or more	11
Dead, intercurrent disease, no signs of tumour	4
Dead, generalized metastases, no signs of local recurrence or lymph node metastases	3
Recurrence within irradiated volume (nasopharynx or neck)	17
Neck node metastases within unirradiated volume but no recurrence within irradiated volume	5
Of the latter 5 patients, 3 lived free from disease 5 years or more after new treatment, one died in gastric carcinoma after 3½ years without signs of original tumour disease and one died with generalized metastases	
Only the last mentioned patient could theoretically have been cured by prophylactic neck irradiation	

Discussion

With regard to the great geographic variations in the incidence of nasopharyngeal tumour, it was of interest to compare the Umeå series from northern Sweden with the country as a whole. No major differences were found, however, concerning annual incidence, male/female ratio and age distribution. Obviously Sweden can be regarded as a fairly homogenous region for this tumour.

The treatment results and the prognosis were in the present series remarkably good and better than in most other series reported. In the very large series from Radiumhemmet from 1937 to 1964 (660 cases) a crude five-year survival of about 30 per cent was obtained (DE SCHRYVER et coll. 1971). In a series of 124 patients, LEDERMAN reported a crude five-year survival of 17 per cent. Some more recently published series have a higher five-year survival: ATKINSON & SCOTT (1967) 28 per cent, PEREZ et coll. (1969) 34 per cent, and MEYER & WANG (1971) 38 per cent. In the present series a crude five-year survival of 43 per cent was obtained. It seems very likely, however, that different series differ considerably as regards the composition, which makes direct comparison impossible. It also seems likely that the results have gradually improved, due to better understanding of the disease, improved treatment technique and earlier diagnosis.

In the present series an evident correlation was found between the extension of the disease and the prognosis. This correlation existed both regarding the extension of the primary tumour and the neck node metastases. Some other authors have previously reported that the occurrence of lymph node metastases does not influence prognosis (LEDERMAN, BERTELSEN et coll.).

The question about irradiation of uninvolved neck sides or not, is still controversial. In the present series as a rule only involved neck sides were irradiated and a retrospective analysis showed that prophylactic irradiation could have added very little or nothing to the curability. Prophylactic neck irradiation would have meant irradiation of 50 more neck sides in 40 patients, which of course would have

increased radiation morbidity considerably In a medically well developed region with good possibilities for follow up of all patients, prophylactic irradiation of the neck does not seem necessary The situation may, however, be quite different in a less developed region, where the cases generally are more advanced and where possibilities for follow up are poor

SUMMARY

A material of 61 malignant nasopharyngeal tumours were treated during the 10-year period 1959-1968 The primary tumour was in most cases treated with a supervoltage technique and *the neck node regions were irradiated only when lymph metastases were found* The crude 5 year survival in the whole series was 43 % and the symptom free 5 year survival 34 % If the rare tumour types were excluded (plasmocytoma and salivary gland type adenocarcinoma) the corresponding figures were 41 and 33 %, respectively The retrospective analysis did not indicate that prophylactic neck irradiation could have increased the cure rate

ZUSAMMENFASSUNG

Ein Material von 61 malignen Nasopharynxtumoren während der 10-Jahres Periode 1959 bis 1968 wurde behandelt Der Primärtumor wurde in den meisten Fällen mit der Hochvolttechnik behandelt und die cervikalen Lymphknoten nur bestrahlt, wenn Meta stasen vorlagen Die grobe 5 Jahres Überlebensrate der ganzen Gruppe betrug 43 % und die symptomfreie 5 jährige Überlebensrate 34 % Wenn seltene Tumoren ausgeschlossen wurden (Plasmocytome und Adenokarzinome vom Speicheldrusen Typus) betrugen die entsprechenden Ziffern 41 % bzw 33 % Die retrospektive Analyse gab keinen Hinweis darauf, dass die prophylaktische Bestrahlung der Lymphknoten die Heilungsrate verbessern konnte

RÉSUME

Une série de 61 tumeurs nasopharyngiennes malignes ont été traitées au cours de la période de 10 ans allant de 1959 a 1968 La tumeur primitive a ete traitée dans la plupart des cas par une technique à supervoltage et les aires ganglionnaires cervicales ont eté traitées seulement quand il y avait des métastases lymphatiques Le taux brut de survie a 5 ans sur l ensemble de la série a été de 43 % et la survie à 5 ans sans symptome a eté de 34 % Si on exclut des types de tumeur rares (plasmocytome et adenocarcinome à type de glande salivaire) les taux correspondants sont de 41 et 33 % respectivement L'analyse retrospective n a pas montré une augmentation du taux de guérison due à l irradiation prophylactique du cou

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TREATMENT OF METASTASES IN NEPHROBLASTOMA

B JEREB and L ÅHSTRÖM

The metastatic disease in nephroblastoma may consist of microscopic or macroscopic metastases, which influences the mode of treatment

For the treatment of microscopic metastases the term prophylactic chemotherapy is used in this report The only means at present to treat microscopic metastases successfully is multidrug therapy as in other malignant tumors such as Ewing's sarcoma (ROSEN et coll 1974), rhabdomyosarcoma (GHAVIMI et coll 1973), and as indicated in nephroblastoma in the National Wilms' Tumor Study (State Center, Seattle, Washington, D'ANGIO 1974) Single drug chemotherapy has not been successful in preventing metastases in nephroblastoma (JEREB & EKLUND 1973) Multidrug chemotherapy is, however, prolonged and not without harm to the patient The question therefore arises of how to distinguish the patients with high risk for spread of disease from those with low risk, in whom prophylactic chemotherapy may not be necessary

In patients with macroscopic metastases, marked improvement in the treatment results has been achieved in recent years This is considered to be due to more active and intensive treatment (SCHWEISGUTH & SCHLINGER 1967, VIETTI et coll 1970) A higher survival rate was achieved when at least two methods of treatment were [illegible] 1966 and 1973 [illegible] reported here

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The results in 36 patients with nephroblastoma admitted between 1966 and 1973 were analysed and are reported here

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Material and Methods

Nineteen of the 36 children were girls, 17 were boys, the youngest child seven months and the oldest ten years old

The primary treatment was rather uniform during these years Patients in stages I and II received postoperative irradiation to the tumor bed, those in stage III were given irradiation to the entire abdomen with shielding of the opposite kidney after 15 Gy (1 500 rad) In addition, patients in stage III were given multiple courses of Actinomycin D during 15 months In stages I and II a single course of Actinomycin D was administered at the time of operation and during five consecutive days The total dose per course was 75 gamma per kg body weight

Fifteen patients developed metastases after completing the primary treatment In 10 patients the metastases were diagnosed within 6 months, in 4 between 6 months and one year and in one patient 16 months after completion of the primary treatment Pulmonary metastases were found in 9 patients multiple and bilateral in 8 and in one patient a solitary metastasis Two patients had multiple metastases to the skeleton, 2 had pulmonary metastases and abdominal recurrences, one had metastases in the liver and in one patient the tumor was growing outside the treatment area per continuitatem Two cases might be of interest

Case 12 (Table 2) A 7-year old boy with a right nephrectomy performed for a Wilms tumor in June 1965, the tumor invaded the surface of the liver and this part of the liver was resected together with the tumor and the right kidney Microscopy revealed a tumor of type III with features of embryonal rhabdomyosarcoma Postoperative irradiation to the tumor bed was started, but was discontinued because of progressive bone marrow depression At that time it was revealed that the patient by mistake had received a double dose of Actinomycin D through the whole course which started on the day of the operation Wide spread metastases in the sekeleton were found 6 weeks after surgery The patient died one month later, two months after admission

Case 15 This 4 year-old boy had on admission a large fixed, inoperable tumor in the right kidney After 20 Gy (2 000 rad) in 2 weeks the tumor decreased considerably in size Nephrectomy was performed 3 weeks after end of irradiation The tumor was found to be growing continuously to the renal vein and the vena cava These masses were removed together with the encapsulated part of the tumor Postoperatively 15 Gy (1 500 rad) were given to the tumor bed the total dose being 35 Gy (3 500 rad) in 50 days The patient received two courses of Actinomycin D at the same time as the irradiation Microscopically the tumor was of type I Further courses of Actinomycin D were discontinued because of irradiation hepatitis Seven months after the last treatment the patient presented with severe respiratory distress Cardioangiography demonstrated a tumor in the right atrium and ventricle of the heart obstructing the pulmonary blood flow At surgery a tumor was found growing along the vena cava into the heart The tumor was removed but the patient died of cardiac failure 24 hours after operation

Of the 15 patients who developed metastases one was not treated for metastases (case 12), one was only operated upon (case 15), the remaining 13 patients were treated with irradiation and chemotherapy, in addition 4 were operated upon When pulmonary metastases were diagnosed, the whole lung was irradiated (16 Gy (1 600

Table 1

Nephroblastoma Thirty-five patients (in one patient the type of tumor was not classified) with localized disease on admission Rate of metastases according to stage and microscopic type of tumor

Stage	Microscopic type			
	I and II		III	
	No of cases	With metastases	No of cases	With metastases
I and II	19	0	7	5
III	5	5	4	4
Total	24	5	11	9

rad) in 11 fractions) and at the same time a treatment course with Actinomycin D was started and continued for 15 months Surgery was reserved for residual or recurrent solitary metastases after irradiation and chemotherapy One patient had four thoracotomies (case 5) In patients who prophylactically received Actinomycin D at the primary treatment Vincristine was given for treatment of the metastases, to those who had not received Actinomycin D primarily this was given alone or together with Vincristine

Results

Of the 36 patients 27 are free of disease, 21 after primary treatment, 6 after treatment of metastases, 9 have died of metastases

All stage III patients developed metastases (Table 1) Three patients who had been classified as stage III only because of involved paraaortic lymph nodes have developed metastases The 5 patients in stages I or II who developed metastases had a tumor of type III None of the patients in stages I or II and with microscopic type I or II developed metastases

Of the 15 patients who were treated for metastases after completing the primary treatment 6 have been free of disease for 2 years or more The 6 survivors had pulmonary metastases and have been treated with chemotherapy and irradiation or surgery (Table 2)

Discussion and conclusions

The most important factor influencing the disease-free survival or, in other words, the rate of metastases, is the stage of the disease, the second factor for all stages is the microscopic type of the tumor (JEREB & SANDSTEDT 1973) The rate of metastases in patients of stages I and II and microscopic type I was extremely low The result of the present series is in accordance with the previous results, although the number of patients is small None of the 19 patients in stages I and II and with tumors of

Material and Methods

Nineteen of the 36 children were girls 17 were boys the youngest child seven months and the oldest ten years old

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are free of disease, while all the 6 patients with metastases in other organs are dead

The risk that patients with nephroblastoma will developed metastases is related to the stage and the microscopic type of the tumor To prevent metastases, multidrug chemotherapy should be used, but should probably be reserved for the high risk patients, those in either stage III or with tumors of microscopic type III The outcome of the disease after the patient has developed metastases is dependent on their location—those with pulmonary metastases having a better prognosis—and on the treatment The treatment of metastases should be combined, and in most cases performed to the limit of tolerance

SUMMARY

A series of 36 children with nephroblastoma treated between 1966 and 1973 was analysed None of the patients with stages I or II and microscopic type I or II developed metastases, 5 of 7 patients with stages I or II and microscopic type III developed metastases All patients in stage III developed metastases Fifteen patients developed metastases after the termination of the primary treatment Of 9 patients with pulmonary metastases only, 6 are free of disease all patients with metastases in other sites are dead

ZUSAMMENFASSUNG

Es wurde eine Serie von 36 Kindern mit Nephroblastom, die zwischen 1966 und 1973 bestrahlt worden waren, analysiert Keiner der Patienten in den Stadien I oder II und den mikroskopischen Typen I und II entwickelte Metastasen, 5 von 7 Patienten im Stadium I oder II und mit einem mikroskopischen Typ III entwickelten Metastasen 15 Patienten entwickelten Metastasen nach Beendigung der primären Behandlung Von 9 Patienten mit nur Lungenmetastasen waren 6 frei von Krankheit, alle Patienten mit Metastasen in anderen Organen sind tot

RESUMÉ

Les auteurs étudient une série de 36 enfants atteints de néphroblastome et traites entre 1966 et 1973 [illegible]
présenté de mé [illegible]
eu des métast [illegible]
eu des métast [illegible] ...ement primaire Sur 9 malades atteints seulement de métastases pulmonaires 6 sont en bonne santé, tous les malades ayant des métastases dans d autres localisations sont morts

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Table 2

Nephroblastoma. Fifteen patients with metastases after primary treatment

Case	Age (years)	Appearance of metastases (months) after primary treatment	Location S = solitary M = multiple	Treatment of metastases	Comment
1	5	2	Lung (S)	R + VCR	NED > 7 years
2	2	6	Lung (M)	R + AMD	NED > 7 years
3	2	3	Lung (M)	R + AMD + Cytox	Dead
4	4	16	Lung (M)	R + VCR + Op	NED > 4 years
5	4	7	Lung (M)	R + AMD + VCR + Op (4 ×)	Dead
6	3	11	Lung (M)	R + VCR	NED > 3 years
7	5	5	Lung (M)	R + VCR	NED > 2 years
8	1	4	Lung (M)	R + Op + VCR	NED > 2 years
9	6	5	Lung (M)	R + AMD + VCR	Dead
10	1	3	Skel (M)	R + AMD + VCR	Dead
11	2	7	Liver	R + VCR	Dead
12	7	1	Skel (M)	—	Dead
13	6	6	Lung (M) + liver	R + AMD + VCR	Dead
14	4	7	Abd lgl + lung (M)	R + AMD + VCR + Op	Dead
15	2	9	Heart	Op	Dead

R = irradiation, Op operation AMD = Actinomycin D, VCR = Vincristine NED = no evidence of disease

microscopic type I or II developed metastases, against 5 of the 7 patients with tumors of microscopic type III (Table 1) Prophylactic administration of Actinomycin D alone did not prevent the spread of the disease in patients in stage III In one patient (case 15) in stage III and with a tumor of type I the cause of death was locally advanced growth of the tumor and not dissemination This suggests that in patients with advanced tumors of microscopic type I local control of the tumor might be more essential than control of possible dissemination

One of the potential complications of chemotherapy is the immuno-suppressive effect, clinically sometimes evident as a life-threatening disease after virus infection In one patient (case 12) the unusually malignant outcome of the disease might be ascribed to an immunosuppressive effect following overdose of Actinomycin D

It has been shown previously that two factors are of significance for the survival rate in patients with metastases Their location and the treatment Patients with only pulmonary metastases treated with combined methods had the highest survival rates (JEREB) The results of the present series confirm the observation that the site of the metastases is of importance Six out of the 9 patients with pulmonary metastases only

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EFFECTS OF IONIZING RADIATION ON THE ACTIVITY OF THE CILIATED EPITHELIUM OF THE TRACHEA

L BALDETORP, D HUBERMAN, C H HÅKANSSON and N G TOREMALM

The late effects of ionizing radiation on the mucociliary activity of the tracheal epithelium have been thoroughly investigated in patients who had been irradiated for bronchial carcinoma or Hodgkin's disease (RUCKES & HOLLSTEIN 1968, FERNHOLZ & MULLER 1969, BOUSHY et coll 1970, LANDBERG et coll 1972), and also in experiments on the rabbit (DANIELSSON et coll 1971) Both the production of mucus and the ciliary activity were reduced by irradiation The duration of the effects was related to the absorbed dose The effects of irradiation on the movements of the cilia have been investigated previously using different methods (UMEDA 1927, HEINE 1936 FRENCKNER 1939, OGI 1959, FUJIWARA et coll 1972) but the immediate effects are largely unknown and controversial

Therefore, it was felt to be of interest to attempt to record the immediate physiologic effects of irradiation on the tracheal mucous membrane from rabbit in vitro using a light reflection method (MERCKE et coll 1974), which registers the mucociliary activity The physiology of the tracheal epithelium has been investigated previously by HÅKANSSON & TOREMALM (1965–1968) their results constitute the background for the evaluation of the effects of irradiation in the present report

Methods and Materials

The trachea of the rabbit has been used in all experiments A total of 20 animals were used, 5 for each dose level The animals were killed by a blow on the skull The

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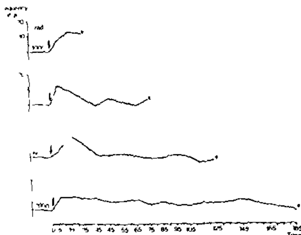


Fig. 2. Mucociliary wave frequency in the trachea after ionizing irradiation at different dose levels (1 Gy 100 rad) Time in seconds

ration and in lead shielded control preparations placed in the chamber on each irradiation The following doses were given 10, 30, 60 and 70 Gy (1 000, 3 000, 6 000 and 7 000 rad), respectively, with continuous registration of the mucociliary activity and the contractions and relaxations of the musculature Sections from the irradiated epithelium and the control sample were taken for scanning electron microscopy (SEM) and transmission electron microscopy (TEM) immediately after the end of irradiation and fixed in glutaraldehyde

Results

The mucociliary activity increased at all dose levels within 5 seconds after the start of irradiation (Fig 2) A return to the level registered before irradiation (reference value) took place after 35 s for 30 Gy, after 65 s for 60 Gy, and after 185 s for 70 Gy For 10 Gy the exposure was too short to permit adequate observation

The mean value could be derived from the observations in the entire series of 20 animals during the first 15 s of the irradiations (Fig 3), as the dose rate was the same at all dose levels and exposures The average increase in frequency after 5 s was 8 ± 2 per cent The maximum increase in frequency occurred after 10 s and was 11 ± 1 per cent after 15 s the increase was 7 ± 2 per cent

As it is important to establish how this frequency increase reflects the biologic processes causing the response to irradiation, the variations of the frequency increase have been analysed in detail This has been done from the basis of the reference value before start of irradiation and by aid of a computer The k-value has been calculated in five second intervals for 0 to 5, 5 to 10 and 10 to 15 s after start of irradiation (Fig 4) The regression line is built up of 6 dots in each interval The k-value for the first 5 s which is 0 82, is followed by a k value of 1 40, and the third k-value (be-

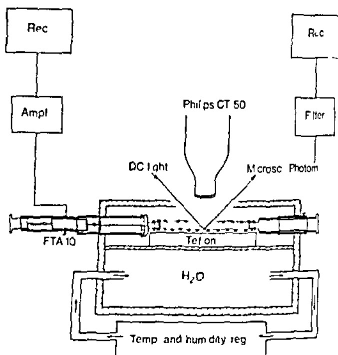


Fig 1 Experimental chamber with the possibilities for simultaneous irradiation and recording

trachea was then immediately dissected and placed on a layer of teflon in an experimental chamber where an even temperature and humidity could be maintained at the level desired (Fig 1) The preparations, on an average 3 5 cm long, were placed in the chamber between two identical adjustable holders and stretched out to their calculated natural length The trachea was then opened by a longitudinal incision in the membranous part, which was turned upwards in the chamber Humidity was kept constant above 90 per cent to prevent drying out, and the temperature was maintained at 30°C The mucociliary activity was registered with a 'light beam reflection method' (HÅKANSSON & TOREMALM 1965, MERCKE et coll) Heat filtered DC light from a cold light source (Zeiss KL 150) illuminated the mucous membrane of the trachea via the incision and was reflected by the mucous ciliary border at the 'bottom' of the trachea The blinking light reflection which arose thereby due to the mucociliary activity was observed through a laboratory microscope A photomultiplier attached to the lens of the microscope was connected to an ink plotter (Mingograf 34, Siemens-Elema) through a frequency filter (Krohn-Hite 3550) This apparatus enabled registration and documentation of the intensity variations of the light reflexes The contractions and relaxations in the preparation were registered continuously by aid of a transducer (Sanborn FTA 10) connected to a plotter (Servogor RE 511)

The preparation was irradiated by Philips' contact therapy apparatus at 50 kV, 2 mA, HVL 0 5 mm Al, focus-object distance 40 mm, dose rate 0,34 Gy/s (34 rad/s) The administered dose was measured in the chamber using thermoluminescent dosemeters (TLD) placed at the bottom of the trachea, on a teflon sheet under the prepa-

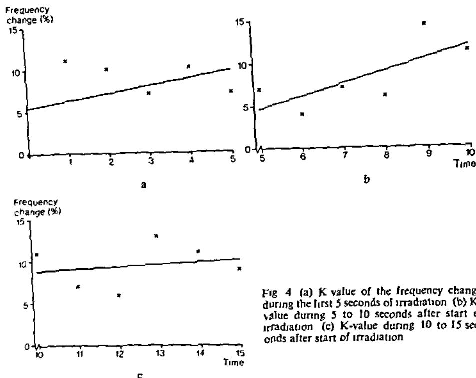


Fig 4 (a) K value of the frequency change during the first 5 seconds of irradiation (b) K-value during 5 to 10 seconds after start of irradiation (c) K-value during 10 to 15 seconds after start of irradiation

The present method enables continuous registration of the epithelial mucociliary activity thus permitting an analysis of the influence of ionizing radiation on the functions of the epithelial cells second by second Under stable conditions the mucociliary activity increased initially after the beginning of irradiation, discernible after 2 to 3 s, reaching its maximum after 10 s and then returning to the original activity. This occurred after a varying time, up to 185 s after beginning of irradiation

The mechanism behind the initial effects of irradiation are not known but some theoretical factors may be considered The cilia require adenosine triphosphate (ATP) as a source of energy for their activity ATP is produced by the mitochondria, which usually lie apically in the epithelial cells Diffusion of ATP is assumed to take place towards the rootlet of the axoneme A suitable concentration of ATP and certain essential ions are maintained around the axoneme through the function of the ciliary membrane The ATP concentration is believed to determine the beat frequency of the cilia (SATIR 1974) Ionizing radiation may cause injuries to the mitochondria resulting in an increased outflow of the ATP available to the cilia It may influence the dyneinmolecules, which are attached to the axoneme and which are active in breaking down ATP into ADP (adenosine diphosphate) and phosphoric acid, whereby energy is released HAMBERGER et coll (1970) have observed an increase of succinoxidase activity in isolated nerve cells as soon as one hour after 30 Gy

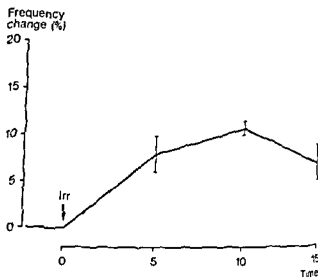


Fig 3 Mucociliary wave frequency during the first 15 seconds of irradiation at a dose rate of 0 34 Gy/s (34 rad/s)

tween 10 and 15 s) was 0 26 The analysis indicated a higher influence, i e a higher response, in the cell during the second phase, that is after 5 to 10 s of irradiation

Changes of contractions and relaxations of the tracheal musculature were registered in approximately 30 per cent of the experiments These changes arose immediately following irradiation (These results as well as the observations from SEM and TEM of the irradiated mucous membrane, will be described in future publications)

Discussion

The ciliated epithelium of the trachea is an ideal object for analysing the effects of irradiation The apical cilia of the epithelial cells maintain constant activity for at least 3 hours after the trachea has been extirpated and placed in an experimental chamber (FUJIWARA et coll) and their activity can be registered (MERCKE et coll, TOREMALM et coll 1974) Thus it is possible, by recording the changes in the mucociliary activity during that length of time, to analyse the effects of ionizing radiation on the vital activity of the living cells

Previously it has been demonstrated that the effect on the movements of the cilia is related to the dose and that high doses are necessary to obtain complete inhibition of the movements (GOLDHABER & BACK 1941) FUJIWARA et coll reported reduced mucociliary activity 15 min after irradiation The activity normalized within 1 5 and 2 5 hours following doses of 5 and 30 Gy (500 and 3 000 rad), respectively After a dose of 70 Gy (7 000 rad) no recovery of ciliary activity occurred during 3 h observation Similar results have previously been published by OGI, no observations of the immediate effects were made HEINE observed an increased beating frequency of the cilia shortly after exposure of the tracheal mucous membrane to radium but this could not be reproduced by exposure to roentgen rays

SUMMARY

The immediate effect of ionizing radiation on the activity of the ciliated epithelium of the trachea has been investigated using a light reflection method This method enables continuous registration of the mucociliary activity both during and after irradiation A notable increase of the mucociliary activity occurred within 5 seconds after beginning of irradiation and this activity reached its maximum 10 seconds after initial exposure with a dose rate of 0 34 Gy/s (34 rad/s) The mechanism causing the phenomena observed is not clear but theoretically it might be due to ATP, the source of energy of the cilia being freed by the irradiation possibly through disturbances of the permeability in the mitochondrion membranes

ZUSAMMENFASSUNG

Der unmittelbare Effekt ionisierender Strahlen auf die Aktivität des Zilienepithels in der Trachea ist mit Hilfe einer Lichtreflexionsmethode studiert worden Diese Methode ermöglicht eine kontinuierliche Registrierung der mucoziliaren Aktivitat sowohl wahrend als auch nach der Bestrahlung Eine bemerkbare Zunahme der mucoziliaren Aktivität erfolgte innerhalb von 5 Sekunden nach Beginn der Bestrahlung Diese Aktivitat erreichte ihren Hochstwert nach einer Expositionszeit von 10 Sekunden mit einer Dosisrate von 0 34 Gy/s (34 rad/s) Eine ursächliche Erklärung fur die beobachteten Erscheinungen steht noch aus Eine theoretisch mogliche Energiequelle fur die Zilienaktivitat ware ATP, das durch die Bestrahlung freigesetzt wird moglicherweise durch Storungen in der Membranpermeabilität der Mitochondrien

RÉSUME

L effet immédiat de radiations ionisantes sur l activité de l epithelium cilie de la trachée a éte étudié en utilisant une méthode de reflexion de la lumière Cette methode permet [illegible]

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(3 000 rad) and an increase of ^{3}H-leucine incorporation into proteins soon after the beginning of irradiation It may be due to an increase in the enzyme content of the cells, or be caused by an activation of previously existing enzymes However, it is also possible that ionizing radiation destroys the physiologic intracellular barriers and thereby influences the enzyme activities It is possible that the observations are expressions of compensating intracellular metabolic processes, replacing the consumed energy in the epithelial cells during irradiation

Microdosimetry has shown that the specific energy which certain particles deposit in some of the subcellular structures may have a range between almost zero to several hundred rad (LINDBORG & BENGTSSON 1973) Such a localized deposit of energy could possibly change the energy status of the cilia However, in these experiments the energy thus brought to a cell is probably quite small

ECKERT & MURAKAMI (1972) found that the beating frequency of the cilia was directly dependent on the concentration of energy available, probably ATP Their finding was confirmed by SATIR They also demonstrated that the beat frequency of the cilia was related to the concentration of intracellular calcium when the calcium concentration increased, the beat frequency also rose Calcium is assumed to influence one or several metabolic steps in the production of ATP by aiding in uncoupling oxidation and phosphorylation, whereby energy is released as heat It may be that ionizing radiation affects the permeability of the cellular and mitochondrial membranes, resulting in an intracellular redisposition of calcium, which in turn affects the ciliary activity On the other hand, increased extracellular calcium ions are known to decrease the velocity of the action potential and to make the membrane more resistant to stimulation (AXELSSON 1961) Electromagnetic radiation of a wavelength different to the roentgen radiation used in the present material is believed to affect the ciliary activity SAIER & GIESE (1966) found increased beat frequency of the cilia of the *Protozoa paramecium* initially after irradiation with ultraviolet light With the low energy spectrum used in the present experiments, excitation phenomenon cannot be excluded

The time elapsed from the beginning of irradiation until the maximum effect is reached is of great interest The maximum appears in the second period (Fig 4 b) This problem covers many unknown parameters, such as different capacity, membrane sensitivity etc , and requires further investigation

It seems to be worthwhile to apply the method presented to an analysis of the influence of the dose rate, different radiation energies and temperature on the effects of ionizing radiation on vital tissues Such investigations may be of value for the clinical radiation therapy

Acknowledgement

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SUMMARY

The immediate effect of ionizing radiation on the activity of the ciliated epithelium of the trachea has been investigated using a light reflection method. This method enables continuous registration of the mucociliary activity both during and after irradiation. A notable increase of the mucociliary activity occurred within 5 seconds after beginning of irradiation and this activity reached its maximum 10 seconds after initial exposure with a dose rate of 0.34 Gy/s (34 rad/s). The mechanism causing the phenomena observed is not clear but theoretically it might be due to ATP, the source of energy of the cilia being freed by the irradiation possibly through disturbances of the permeability in the mitochondrion membranes.

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Der unmittelbare Effekt ionisierender Strahlen auf die Aktivität des Zilienepithels in der Trachea ist mit Hilfe einer Lichtreflexionsmethode studiert worden. Diese Methode ermöglicht eine kontinuierliche Registrierung der mucoziliaren Aktivität sowohl *während als* auch nach der Bestrahlung. Eine bemerkbare Zunahme der mucoziliaren Aktivität erfolgte innerhalb von 5 Sekunden nach Beginn der Bestrahlung. Diese Aktivität *erreichte ihren Hochstwert* nach einer Expositionszeit von 10 Sekunden mit einer Dosisrate von *0.34 Gy/s (34 rad/s)*. Eine ursächliche Erklarung fur die beobachteten Erscheinungen *steht noch aus*. Eine theoretisch mogliche Energiequelle fur die Zilienaktivität wäre ATP, das durch die Bestrahlung freigesetzt wird, moglicherweise durch Storungen in der Membranpermeabilität der Mitochondrien.

RÉSUMÉ

L'effet immédiat de radiations ionisantes sur *l'activite de l'épithelium* [illegible]
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VARIATION OF THE RELATIVE BIOLOGIC EFFECTIVENESS WITH TUMOR SIZE USING ACCELERATED HELIUM IONS

J SHAEFFER, A M EL MAHDI, H ACETO, JR and W C CONSTABLE

The use of accelerator produced particle beams in the radiation therapy of human tumors is a subject of considerable current interest Due to certain geometric and biologic features such beams may be able to provide important advantages resulting in improved local control of circumscribed malignant neoplasms

Clinical trials using high LET radiation sources have concerned themselves primarily with advanced cases of neoplasia (CATTERALL & VONBERG 1974, KAPLAN 1971 KLIGERMAN 1971) Ethical considerations notwithstanding, the scientific rationale for choosing advanced cases is that these tumors would be expected to contain larger percentages of hypoxic cells which could be killed more effectively by high than by conventional low LET irradiation This communication addresses itself to the question of how RBE might vary with the size of the tumor being irradiated using accelerated helium ions

When injected intravenously into tumor free isogeneic C3H/He mice, cell suspensions from the Dunn osteosarcoma result in the formation of pulmonary colonies or metastases Animals with such metastases were irradiated thoracically using either a ^{60}Co teletherapy unit or a therapeutic helium ion beam which is currently being used

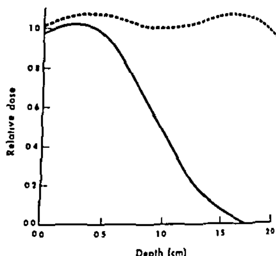


Fig 1 Relative depth dose of the acceler ated helium ion beam from a single field (solid line) and computed for parallel op [illegible]

clinically (D'ANGIO et coll 1974) at the Space Radiation Effects Laboratory (SREL) Mice were treated at 1, 7 or 14 days after tumor cell injection, at which times the average tumor volumes were approximately 5×10^{-5}, 1×10^{-3}, or 1×10^{-2} mm³ In addition, single cell suspensions of the tumor were irradiated by both modalities be fore intravenous injection Results were evaluated by comparing the number of lung colonies in the irradiated groups to those of sham-irradiated controls

Materials and Methods

The source and maintenance of mice as well as method of preparing tumor cell suspensions have been previously described (SHAEFFER et coll 1973 a, 1974) Tumor-free mice were injected in the tail vein with about 1×10^7 total cells in 0 4 ml This inoculum resulted in approximately 100 metastatic lung colonies per mouse when untreated (control) animals were killed 30 days after tumor cell injection Both the time of appearance of lung colonies and their growth rates have been previously re- ported (SHAEFFER et coll 1974)

⁶⁰Co irradiation A ⁶⁰Co teletherapy unit operated at 80 cm source-tumor distance was used as the low LET source for animals irradiated in vivo The dose rate in tissue was approximately 1 Gy/min (100 rad/min) at the mid-thoracic plane The thoracic region, with an anteroposterior diameter of 1 96 cm, was irradiated by a single anterior field using bolus Anesthetized mice (0 07 mg sodium pentobarbital per gram body weight administered i p) were irradiated in groups of 8 with a 2 6 cm × 23 cm port The same field size was used for the helium ion beam The untreated areas of the animals were shielded with 7 HVT of lead Single mid thoracic doses ranging from 3 5 to 17 5 Gy (350 to 1 750 rad) were used Midline tissue doses are based on midline doses in air as determined by NBS, using an appropriate air-tissue conversion factor and depth-dose correction

Tumor cell suspensions were irradiated in vitro with ⁶⁰Co as previously described

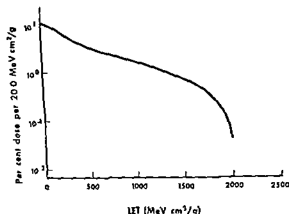


Fig 2. LET spectrum of the helium ion beam at a 1 cm depth in a water phantom. The integral of the per cent of dose is presented as a function of particle LET

(SHAEFFER et coll 1973 b) with a dose rate of 0 92 Gy/min (92 rad/min) at the center of the test tube Suspensions were kept in an ice bath to minimize cell death at a concentration of $2\ 5 \times 10^7$ cells/ml and were intravenously injected into tumor-free mice within 1 hour after irradiation or sham irradiation

Helium ion irradiation The doubly charged helium ion beam at the SREL-synchrocyclotron (Newport News, Virginia) was used A relatively monoenergetic 710 MeV primary helium ion beam was degraded to a broad range of low energies resulting in the transformed depth-dose distribution (Fig 1, solid line) This transformation was achieved through the use of an appropriately designed multiple thickness degrader, or ridge filter' Helium ions ranging from near zero energy to a residual energy of 187 MeV, corresponding to a maximum penetration depth of 1.96 cm in tissue equivalent material, were transmitted through the filter

Measurements of the LET distribution were made at several positions along the depth-dose curve Energy spectrum measurements were made at each position using silicon diode From these data, the corresponding LET spectrum was determined Fig 2 depicts one such measurement performed at 1 cm depth in a water phantom This figure, expressing the integral of the per cent of dose as a function of particle LET, indicates that for 1 cm depth of penetration, nearly 20 per cent of the absorbed dose is delivered by particles of LET greater than 100 KeV/μ

Measurement of depth-dose was performed with a miniature ionization chamber which was remotely scanned in a tissue-simulating water tank Procedures for absolute measurement of dose and beam monitoring involved standard ionization chambers as described previously (EL-MAHDI et coll 1974)

Anesthetized animals were arranged in a specially constructed lucite holder and positioned in the beam The holder was so constructed as to provide irradiation of the thoracic region only The prescribed midline tissue dose was delivered using two parallel and opposed ports The time interval between the treatment of the opposing fields was less than 5 min The depth-dose distribution across the thoracic region



Fig 3 Gross appearance of heart and lungs of C3H/He mouse killed 42 days after injection of 4×10^4 Dunn osteosarcoma cells Pulmonary colonies are easily distinguishable by naked eye

which results from the addition of two opposing radiation fields is given in Fig 1b (broken line)

Helium ion doses ranging from 3 5 to 17 5 Gy (350 to 1 750 rad) were delivered to the midthoracic plane at a dose rate of about 1 Gy/min (100 rad/min) Positions intermediate to the surface and midline of the animals received doses no greater than about 8 per cent higher than the mid-thoracic dose (Fig 1, broken line)

Tumor cell suspensions for in vitro helium ion irradiation were placed in 5 ml pipets and positioned in a tissue-simulating water phantom The dose rate at the center of the pipet was 1 2 Gy/min (120 rad/min) Cell concentrations, handling and injections were the same as previously mentioned for the ^{60}Co-irradiated tumor cell suspensions

All animals were killed 30 days after tumor cell injection and the number of metastatic pulmonary colonies was scored after fixation of the lungs for 24 hours in buffered neutral formalin followed by a 5 day storage in 80 per cent ethanol to maximize the contrast between normal and neoplastic tissues (Fig 3)

Results

Lung colony numbers for mice treated at 1, 7 or 14 days after i v tumor cell injection are summarized in Table 1 Of the 392 mice irradiated or sham-irradiated, 364 were used for lung colony determinations The remaining 28 mice died from anesthesia, succumbed from the tumor before 30 days, or were immediately killed because they moved away from the beam during treatment

Table 1

Lung colony numbers in tumor bearing mice treated in vivo at 1, 7 or 14 days by helium ions or ^{60}Co photons

Gy*	Treatment modality	Mean No of lung colonies±SE		
		Rx 1 day	Rx 7 days	Rx 14 days
0 (control)	None	66 9±17 3	181 3±25 8	78 0±15 5
3 5	^{4}He	54 2±25 6	110 1±20 4	47 4± 7 2
	^{60}Co	48 7± 6 8	151 2±25 0	62.4±11 0
7	^{4}He	9 0± 8 2	56 8±13 4	34 4± 4 8
	^{60}Co	17 5± 6 5	108 1±24 2	47 4± 7 5
10	^{4}He	3 2± 2.5	43 2± 7 7	16 5± 3 9
	^{60}Co	6 8± 3 4	74 9±13 5	45 1± 7 9
14	^{4}He	<1	17 6± 6 0	11 9± 4 0
	^{60}Co	<1	33 1± 4 7	29 3± 4 7
17 5	^{4}He	<1	9 0± 6 7	6 3± 2 3
	^{60}Co	<1	28 4± 8 0	16 8± 4 1

* 1 Gy = 100 rad

Mean lung colony numbers for mice injected with tumor cells irradiated in vitro by helium ions or ^{60}Co photons are found in Table 2 Eight mice per group were used

The dose required to reduce the lung colony number to 10 per cent of the control value (D_{10}) was calculated for each treatment group using least squares regression analysis RBE values were thus calculated as the ratio D_{10} (^{60}Co)/D_{10} (^{4}He) Values of D_{10}, RBE, and tumor size are summarized in Table 3

Table 2

Lung colony numbers in mice injected with tumor cells irradiated in vitro by helium ions or ^{60}Co photons

Gy*	Treatment modality	No of mice	Mean lung colonies±SE
0 (control)	None	16	124 7 ±14 3
1	^{4}He	8	67 5 ±14 1
	^{60}Co	8	72.2 ±17 4
5	^{4}He	8	11 2 ± 2.0
	^{60}Co	8	9 1 ± 2.3
8	^{4}He	8	3 38± 0 89
	^{60}Co	8	2.38± 1 10
10	^{4}He	8	0 98± 0 69
	^{60}Co	8	1 12± 0 30

* 1 Gy 100 rad

Table 3

Tumor volumes, D_{10} and RBE values for Dunn osteosarcoma irradited by helium ions or ^{60}Co photons

Age of tumor (days)	Tumor volume (mm^3)	No of cells	Treatment modality	D_{10}, Gy	RBE
0 (in vitro)	1×10^{-6}	1 3*	^4He	4 81	0 97
			^{60}Co	4 66	
1	5×10^{-5}	50**	^4He	7 86	1 2
			^{60}Co	9 33	
7	1×10^{-3}	1 000**	^4He	13 89	1 4
			^{60}Co	19 94	
14	1×10^{-2}	10 000**	^4He	16 27	1 6
			^{60}Co	26 18	

* Based on microscopy of tumor cell suspension in which 500 colony forming units were scored for multiplicity

** Assuming that 1 mm^3 of tumor contains 10^6 cells

Discussion

In comparing the radiation effects of ^{60}Co and helium ions, the most notable aspect of the results is that RBE increased as tumor size increased (Table 3), thereby providing some biologic basis for the selection of advanced cases of neoplasia for clinical trials using high LET radiation sources It is tempting to try to explain these results on the basis of the oxygen effect Although the magnitude of the hypoxic fraction in these tumors as a function of their size is not known, it is not unreasonable to assume that the hypoxic fraction becomes larger as the tumor size increases If this is the case, then the ^{60}Co (low LET) radiation would be progressively less effective against the larger tumors compared to the higher LET helium ion beam, due to the lower OER of the high LET source In vitro determinations of the OER of this beam using HeLa and T-1 kidney cells fall in the range of 1 8–2 0 (unpublished data)

It is not clear how the relative percentages of cycling and non-cycling tumor cells in various sized tumors would affect the overall tumor response differentially Experiments to determine the growth fraction of the Dunn osteosarcoma as a function of tumor size, which are in progress, will hopefully shed some light on the possible relationship between growth fraction and differential tumor response to high and low LET radiation

At the same time, the size effect must also be kept in mind If all the cells in the different-sized tumors were in a 100 per cent oxygenated state, the RBE of the helium ion beam could still vary as a function of tumor size due to the varying number of cells in the target, that is, the number of clonogenic cells per metastatic lesion

It should be mentioned that the present results are somewhat at variance with previous results in which an RBE of 1 47 was reported for a 7 day mammary tumor

($\sim 5 \times 10^{-4}$ mm³) while the RBE for a 14 day tumor ($\sim 2 \times 10^{-2}$ mm³) was 1 25 (El-Mahdi et coll) It must also be noted that the present experiments utilized a different tumor as well as a different helium ion beam Surely, biologic differences such as growth fraction cell cycle times and degree of oxygenation between the two tumors (mammary adenocarcinoma and osteosarcoma) could account for these differences in RBE values On the positive side, it is noteworthy that the values of RBE for the two systems are in good agreement with those reported for the same helium ion beam used to treat patients with mycosis fungoides (D Angio et coll 1974)

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The authors wish to thank Drs Charles W Miller and Robert C McLaughlin Dept of Orthopedics University of Virginia Medical Center for supplying the tumor Thanks are also due Dr Raj Jolly Dave Buckle and Connie Allen for technical assistance

SUMMARY

The RBE of an accelerated helium ion beam was determined on murine osteosarcomas ranging in size from single cells to visibly detectable lung colonies of approximately 1×10^{-2} mm³ That the RBE increased as tumor size increased provides some biologic basis for the selection of advanced cases of neoplasia for clinical trials using relatively high LET radiation sources

ZUSAMMENFASSUNG

Die RBE eines beschleunigten Helium Ionen Strahls wurde an murinen Osteosarcomen im Grössenbereich einzelner Zellen bis zu feststellbaren Lungenkolonien von etwa 1×10^{-2} mm³ bestimmt Di[illegible] bio-logische Basis fur [illegible] Ver-suchen unter Anwe[illegible]

RESUMÉ

L EBR d un faisceau d ions d hélium accélérés a été determinée sur des ostéosarcomes de souris dont les dimensions allaient de cellules isolées jusqu à des colonies pulmonaires visibles d environ 1×10^{-2} mm³ Le fait que l EBR augmente à mesure que la taille de la tumeur augmente donne un argument biologique pour choisir des cas avancés de néoplasie pour les essais cliniques utilisant des sources de radiations ayant un TEL relativement haut

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Table 3

Tumor volumes, D_{10} and RBE values for Dunn osteosarcoma irradited by helium ions or ^{60}Co photons

Age of tumor (days)	Tumor volume (mm^3)	No of cells	Treatment modality	D_{10}, Gy	RBE
0 (in vitro)	1×10^{-6}	1.3*	^4He	4 81	0 97
			^{60}Co	4 66	
1	5×10^{-4}	50**	^4He	7 86	1 2
			^{60}Co	9 33	
7	1×10^{-3}	1 000**	^4He	13 89	1 4
			^{60}Co	19 94	
14	1×10^{-2}	10 000**	^4He	16 27	1 6
			^{60}Co	26 18	

* Based on microscopy of tumor cell suspension in which 500 colony-forming units were scored for multiplicity

** Assuming that 1 mm^3 of tumor contains 10^6 cells

Discussion

In comparing the radiation effects of ^{60}Co and helium ions, the most notable aspect of the results is that RBE increased as tumor size increased (Table 3), thereby providing some biologic basis for the selection of advanced cases of neoplasia for clinical trials using high LET radiation sources It is tempting to try to explain these results on the basis of the oxygen effect Although the magnitude of the hypoxic fraction in these tumors as a function of their size is not known, it is not unreasonable to assume that the hypoxic fraction becomes larger as the tumor size increases If this is the case, then the ^{60}Co (low LET) radiation would be progressively less effective against the larger tumors compared to the higher LET helium ion beam, due to the lower OER of the high LET source In vitro determinations of the OER of this beam using HeLa and T-1 kidney cells fall in the range of 1 8–2 0 (unpublished data)

It is not clear how the relative percentages of cycling and non-cycling tumor cells in various sized tumors would affect the overall tumor response differentially Experiments to determine the growth fraction of the Dunn osteosarcoma as a function of tumor size, which are in progress, will hopefully shed some light on the possible relationship between growth fraction and differential tumor response to high and low LET radiation

At the same time, the size effect must also be kept in mind If all the cells in the different-sized tumors were in a 100 per cent oxygenated state, the RBE of the helium ion beam could still vary as a function of tumor size due to the varying number of cells in the target, that is, the number of clonogenic cells per metastatic lesion

It should be mentioned that the present results are somewhat at variance with previous results in which an RBE of 1 47 was reported for a 7 day mammary tumor

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FALL IN BLOOD PRESSURE DURING RADIATION THERAPY

LARS ERIC LARSSON, JÜRGEN LINDAHL and BERTIL UNSGAARD

Patients irradiated for malignant tumours often experience nausea and vertigo A cause, often overlooked, is the fall in blood pressure and an impaired orthostatic tolerance which some of these patients exhibit (COUTARD & LAVEDAN 1922, LEACH 1943) In the years 1969 to 1971 a major series of patients treated at Radiumhemmet by external irradiation for various malignant tumours was examined regarding complications from the cardiovascular system Some of these patients reported vertigo which they had not had before and 2 patients were brought to the emergency unit following syncope outside the hospital One formerly hypertensive patient got [illegible]

[illegible] of the blood pressure in the supine and standing position in patients treated by external irradiation A considerable fall in blood pressure has occurred in some cases and an attempt to counteract this has been made by administration of dihydroergotamine

Material and Methods

In 176 patients treated during the period September 1970 to October 1971 the blood pressure was recorded in the supine and standing position during and after the period of irradiation

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SHAEFFER J, EL-MAHDI A M and CONSTABLE W C (a) Radiation control of microscopic pulmonary metastases in C3H mice Cancer 32 (1973), 346

— — — (b) Lung colony assays of murine mammary tumor cells irradiated in vivo and in vitro Radiology 109 (1973), 703

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The blood pressure was measured with a standard Riva-Rocci mercury manometer with the auscultatory method of KOROTKOFF (1905) The heart rate was estimated by counting the radial pulse for 30 seconds In order to avoid, as far as possible, psychologic influence on the blood pressure and heart rate, the initial value was not taken the day diagnosis or treatment was announced to the patient and not at the first visit to the treatment department All measurements were made in the same room, with the same manometer and by the same nurse The blood pressure measurement was obtained in all patients on the same arm each time The blood pressure and heart rate were measured after at least 10 min of supine rest on a couch in a separate room A second reading was performed to examine the orthostatic tolerance when the patient had been standing for 8 minutes

In order to avoid that the results will be misleading due to too high an initial value, the changes in blood pressure and heart rate between the initial reading (week 0) and the reading at the end of the first week of treatment (week 1) were calculated and tested for statistical significance separately (paired differences, t test) Linear regression lines for systolic and diastolic blood pressure and for heart rate during the rest of the treatment period were then calculated for each patient in order to eliminate the effect of individually varying absolute blood pressure levels and of missing values on the statistical calculations The blood pressure and heart rate values during the treatment period were assumed to follow linear functions although this assumption was in some cases only approximately correct The mean values of the individual regression coefficients were determined and the trends for the whole group and for different subgroups were tested regarding statistical significance (t-test) The numerical calculations were performed according to conventional computer programs

Results

The mean values of blood pressure and heart rate in supine and standing positions for the whole group of patients are presented in Table 2 The blood pressure at rest, supine, decreased from 136/78 mm Hg before the beginning of the treatment period (week 0) to 132/76 after one week (week 1) and then decreased gradually further to 124/73 mm Hg after 6 weeks of treatment The heart rate was essentially unchanged before and during the treatment period (*mean 76 beats/min*) The corresponding values for the blood pressure in the erect position were 134/88, 128/87 and 124/86 mm Hg, respectively The heart rate was essentially unchanged before and during the treatment period also in the upright position (*mean 89 beats/min*)

The statistical significance of the changes in blood pressure and heart rate tested for all the [illegible]
(Ta [illegible]
occ [illegible] during the treatment period This was found also when the patients were divided into one group with thoracic irradiation and one group with abdominal or pelvic irradiation and when the patients were divided into

Table 1

Material, diagnosis and radiation therapy

Diagnosis	Patients			Tumour dose (rad)	Treatment period (days)
	Number	Age (years)			
		Mean	Range		
Carcinoma of the					
breast	37	55	40–74	4 300–6 500	26–75
oesophagus	8	65	58–77	4 000–6 500	27–70
lungs	3	65	60–74	4 000–5 400	28–53
prostate	8	67	54–77	5 400	40–49
urinary bladder	12	67	59–76	4 100–8 300	31–55
Malignant lymphoma	36*	42	10–79	2 600–4 500	23–63
Seminoma	6	34	29–44	2 000–4 500	14–70
Hypernephroma	4	56	44–74	3 000–4 800	32–50

* Of these 16 treated in the abdominal and pelvic regions only

In the statistical calculation were included 114 patients who fulfilled the following criteria

(1) The initial blood pressure ≤165 mm Hg systolic and ≤95 mm Hg diastolic (age 50 and below) and ≤185 mm Hg systolic and ≤105 mm Hg diastolic (age above 50)

(2) The initial blood pressure taken within 2 weeks before the start of the treatment

(3) The period of treatment at least 3 weeks

(4) Observations from at least two thirds of the treatment period and not missing for more than 2 weeks in succession

(5) No antihypertensive medication during the period of observation

The diagnosis in these 114 patients appears in Table 1 The patients with carcinoma of the breast received either radiation treatment only, or preoperative or postoperative treatment to the axilla, supraclavicular and parasternal region and in some cases also to the tumour region In other cases treatment was given to the parasternal glands only The patients with malignant lymphoma were irradiated, using mantel field, inverted Y-field, other local fields or combinations of these fields The high dose of 8 300 rad to some patients with carcinoma of the urinary bladder was given with superfractionation (LITTBRAND et coll 1975)

Almost all patients were treated at the out-patient clinic and several maintained their professional work during the treatment period

Arterial blood pressure and heart rate were recorded at rest supine and standing before the beginning of the treatment period, at the end of each week during treatment and one and six months after end of the treatment period The patients were usually followed for 4 to 8 weeks of treatment and in 14 cases for up to 14 weeks

Table 4

Statistical significance of the changes in blood pressure and heart rate for the material subdivided by the irradiated anatomic region and by type of tumour

Group	Week 0–week 1 (probability)	Week 1–end of treatment (probability)	End of treatment–1 month after treatment (probability)	End of treatment–6 months after treatment (probability)
Thorax				
Supine				
Systolic	<0 05	<0 001	<0 05	<0 01
Diastolic	<0 05			
Heart rate	<0 05		<0 05	
Standing				
Systolic	<0 01	<0 001		
Diastolic				<0 01
Heart rate				
Abdomen, pelvis				
Supine				
Systolic	<0 01	<0 001		
Diastolic	<0 05			<0 01
Heart rate				
Standing				
Systolic	<0 001	0 01		<0 01
Diastolic			<0 05	<0 001
Heart rate				
Epithelial				
Supine				
Systolic	0 05	<0 001		<0 01
Diastolic		<0 05		<0 05
Heart rate		<0 001	<0 05	
Standing				
Systolic	0 01	<0 001		<0 05
Diastolic		<0 05		<0 001
Heart rate	<0 05	<0 05		
Lymphoma, seminoma				
Supine				
Systolic	0 01	<0 001	<0 05	
Diastolic	0 05			<0 01
Heart rate				
Standing				
Systolic	0 001	<0 01		<0 05
Diastolic				
Heart rate				

Table 2

Mean values of blood pressure and heart rate, supine and standing, during and after radiation therapy in the whole material

Week of treatment	Supine				Standing			
	Number of patients	Blood pressure (mm Hg)		Heart rate (beats/min)	Number of patients	Blood pressure (mm Hg)		Heart rate (beats/min)
		Systolic	Diastolic			Systolic	Diastolic	
0	114	136 ± 17	78 ± 11	76 ± 12	105	134 ± 19	88 ± 10	90 ± 14
1	107	132 ± 19	76 ± 12	75 ± 11	95	128 ± 19	87 ± 12	88 ± 13
2	107	130 ± 19	75 ± 12	74 ± 11	97	127 ± 17	87 ± 11	88 ± 13
3	103	128 ± 19	74 ± 12	76 ± 11	89	126 ± 18	85 ± 12	89 ± 13
4	96	126 ± 16	75 ± 10	75 ± 11	82	126 ± 17	86 ± 11	88 ± 14
5	93	125 ± 17	75 ± 11	76 ± 12	82	125 ± 17	86 ± 10	89 ± 15
6	59	124 ± 15	73 ± 11	78 ± 13	48	124 ± 17	86 ± 10	89 ± 14
1 month after end of treatment period	59	127 ± 16	76 ± 9	78 ± 12	54	126 ± 16	88 ± 9	91 ± 14
6 months after end of treatment period	49	131 ± 16	79 ± 9	76 ± 13	47	130 + 16	90 ± 9	87 ± 15

The standard deviation is given for each mean value

Table 3

Statistical significance of the changes in blood pressure and heart rate in the whole material

	Week 0–week 1			Week 1–end of treatment			End of treatment –1 month after treatment			End of treatment –6 months after treatment		
	$\bar{d}$	p	n	$\bar{\beta}$	p	n	$\bar{d}$	p	n	$\bar{d}$	p	n
Supine												
Systolic	4	<0.001	107	1.09	<0.001	114	+4	0.01	59	+6	0.01	49
Diastolic	−3	<0.01		0.12			+2			+4	0.01	
Heart rate	2	<0.05		0.34	<0.01		+2	0.05		+1		
Standing												
Systolic	5	<0.001	94	0.80	<0.001	88	+4	0.05	54	+6	<0.01	47
Diastolic	−1			0.24			+1			+5	<0.001	
Heart rate	2			0.27			+1			1		

$\bar{d}$ mean of difference, $\bar{\beta}$ – mean of regression coefficients, p probability, n = number of patients

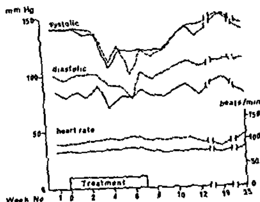


Fig 1 Case 1 Blood pressure and heart rate supine (——) and standing (----)

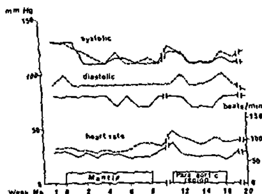


Fig 2 Case 2 Blood pressure and heart rate supine (——) and standing (---)

exhibited considerable reductions in blood pressure which is illustrated by the following case reports

Case 1 A 57-year-old woman with carcinoma of the urinary bladder, T 3, malignant grade IV (UICC, 1974), received 6 480 rad in estimated tumour dose with a 6 MV linear accelerator during 45 days She had a history of incipient cardiac insufficiency (ankle oedema in the evenings, dyspnea and palpitations at moderate exercise) During the treatment these symptoms

supine

and in

taneou ... The blood pressure returned to the pre-treatment level within one month after *irradiation* However, the patient was still troubled with these symptoms which were less evident 6 months after end of treatment

Case 2 A 31-year-old *man without* any previous history of

the start of treatment Du

impaired with dyspnea, p ... moderate exercise Vertigo and nausea occurred when he rised from supine position The blood pressure supine decreased

Table 5

Relation between the extent of the fall in blood pressure, age, and initial blood pressure

Group	Supine				Standing			
	Systole		Diastole		Systole		Diastole	
	Pressure fall related to		Pressure fall related to		Pressure fall related to		Pressure fall related to	
	Age	Initial pressure	Age	Initial pressure	Age	Initial pressure	Age	Initial pressure
All patients	<0.001	<0.001	<0.05	<0.01	<0.01	<0.01		<0.001
Thorax	<0.05				<0.05	<0.01		<0.01
Abdomen, pelvis	<0.05	<0.001	<0.05	<0.05	<0.05		<0.01	<0.01
Epithelial								<0.001
Lymphoma, seminoma	<0.05	<0.001	<0.05	<0.01	<0.05	<0.001		<0.05

one group with epithelial tumours and one group with lymphoma and seminoma (Table 4).

The change in systolic and diastolic blood pressure in supine and standing positions in the course of treatment was correlated to the age of the patient, to the absolute level of the blood pressure, to symptoms in the form of headache and vertigo with or without nausea and to the radiation dose. In the whole group of patients the magnitude of the fall in blood pressure was significantly correlated to the age of the patients and to the absolute level of the initial blood pressure with a more marked fall in blood pressure in older patients and in patients with a higher blood pressure (Table 5). The same observations were made in the groups 'Abdomen, pelvis' and 'Lymphoma, seminoma' but in the group treated with thoracic fields in the upright position only. No correlations were found between change in blood pressure and radiation dose or subjective complaints.

At the follow-up examination one and 6 months after the end of the treatment period, an increase in blood pressure was observed which was statistically significant at least at the 6-month follow-up (Tables 3 and 4). Still, the absolute level for the systolic blood pressure, supine and in the erect position, was below the initial values (Table 2).

The mean values of the decrease in blood pressure are rather small both in the whole material and in the different subgroups and hardly of clinical significance. On examination of the individual cases it was found, however, that major changes (≥25 mm Hg systolic or >15 mm Hg diastolic) occurred in about 25 per cent of the patients, while the majority had only negligible changes in blood pressure. Some cases

and two weeks of irradiation In 5 of these patients a decrease in blood pressure was found (mean value supine 7 mm Hg systolic and 9 mm Hg diastolic, standing 0 mm Hg systolic and 15 mm Hg diastolic) and an essentially unchanged blood volume (mean change +0 2 l) A moderate rise in blood pressure and unchanged blood volume occurred in one patient

Discussion

The material consisted of patients treated for some of the more common types of malignant tumour The established reduction in blood pressure during treatment was on an *average small and in the majority of cases probably without clinical significance* However, in about 25 per cent of the patients a considerable fall in blood pressure was found The separation of patients into one group with thoracic and one with abdominal or pelvic fields irradiated and secondly into one group with epithelial tumours and one with mesenchymal tumours treated was made in order to elucidate the mechanism behind this reaction Statistically significant blood pressure decrease appeared in all subgroups and the fraction of patients with marked blood pressure fall was the same in all the subgroups Hence, the decrease was not correlated to the anatomic region irradiated, neither to minor or extensive tissue break-down connected to the irradiation

As postulated by PIERCE et coll, the weight loss associated with irradiation could be accompanied by a decrease in the blood volume In 6 patients the blood volume was determined to find out if the fall in blood pressure in the present material was correlated to a blood volume reduction A decrease in blood pressure occurred in these patients of the same order as in the patients in the rest of the material, however, the blood volume increased rather than decreased Accordingly, no reduction in blood volume, to explain the changes in blood pressure, could be established in these cases A change in vascular tone, especially on the venous side, due, inter alia to toxaemia, could on the other hand make the blood volume small in relation to the volume of the vascular bed

The decrease in blood pressure could at least in part be due to the fact that the patients got accustomed to the department and the blood pressure measurements It has been shown (DUNNE 1969, ARMITAGE & ROSE 1966) that by repeated blood pressure determinations distributed over several weeks, the blood pressure has a downward trend DUNNE found in untreated hypertensive patients a reduction in blood pressure especially between the first and the *second visit to the outpatient* department ARMITAGE & ROSE found in healthy volunteers, followed during 6 weeks, a downward trend, which only applied to the diastolic blood pressure, however In the present material a statistically significant decrease in systolic as well as diastolic blood pressure was found, not only between the first and the second measurement, but also in the course of the following 4 to 8 weeks Subsequently, some restitution towards the initial blood pressure was found within 6 months after termination of the treatment period

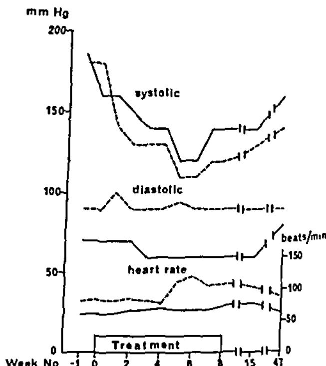


Fig 3 Case 3 Blood pressure and heart rate supine (——) and standing (---)

from 130/80 initially to 110/70 mm Hg and standing from 130/100 to 110/90 mm Hg (Fig 2) Simultaneously the heart rate tended to increase During the 3-week-interruption in treatment the blood pressure almost returned to pre-irradiation levels The heart rate was, however, remarkably high both supine and standing A second fall in the blood pressures occurred during the irradiation of the para-aortic region The symptoms were the same as during the mantle treatment These symptoms remained one month after end of treatment but had mostly disappeared 6 months after the treatment period

Case 3 A 67-year-old woman received preoperative irradiation of a carcinoma of the right breast The irradiation was delivered with a ^{60}Co unit to the primary tumour and the regional lymph nodes (4 800 rad during 50 days), to the axilla (4 500 rad during 41 days) and to the fossa supraclavicularis (4 900 rad during 59 days) She had had angina pectoris and moderate cardiac insufficiency for many years as well as tachycardia and extrasystoles periodically The latter symptoms increased during the period of treatment and dyspnea and periods of tachycardia and extrasystoles occurred also at rest, vertigo and nausea at rise from supine position The blood pressure supine decreased from initially 185/70 to 120/60 mm Hg and standing from 180/90 to 110/95 mm Hg during treatment Simultaneously the heart rate increased from about 60 to about 80 beats/min supine and from about 80 to about 120 beats/min standing Both the supine and the standing blood pressure returned towards the pre-irradiation level after end of treatment, being 140/60 and 130/60 mm Hg at one month and 160/80 and 140/90 mm Hg at 6 months, respectively The heart rate was also normalized (Fig 3)

As a complement to the results presented, blood volume determination was added in a series of another 6 patients who were otherwise treated and examined in the same way as described The blood volume was determined with ^{125}I labelled human serum albumin (Williams & Fine 1961) before the radiation therapy started and after one

and two weeks of irradiation In 5 of these patients a decrease in blood pressure was found (mean value supine 7 mm Hg systolic and 9 mm Hg diastolic, standing 0 mm Hg systolic and 15 mm Hg diastolic) and an essentially unchanged blood volume (mean change +0 2 l) A moderate rise in blood pressure and unchanged blood volume occurred in one patient

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Blood pressure fall in connection with radiation therapy has been described previously by COUTARD & LAVEDAN, who presented four cases, and by LEACH who reported the maximum and average fall in blood pressure in 85 patients In the present material blood pressure falls in a few cases were of the same order as those reported by COUTARD & LAVEDAN On the other hand, the mean value of the decrease in the present material was less than reported by LEACH

One possible explanation of the fall in arterial blood pressure in these patients is a change of tone in the capacitance vessels with venous pooling of blood By improving venous return of blood to the heart the vasoactive drug dihydroergotamine might counteract this fall in blood pressure (MELLANDER & NORDENFELT 1970) Treatment with dihydroergotamine was tried in some patients with marked decrease in blood pressure However, the drug had a satisfactory effect on the subjective complaints in some of the patients only A systematic trial to establish the effect of the drug on the blood pressure in these cases was not carried out

Acknowledgement

Our sincere thanks to Ulf Brodin, B Sc, Computer Department, Karolinska Institutet Stockholm, for performing the statistical calculations and for valuable advice regarding the statistical methods

SUMMARY

Blood pressure and heart rate at rest in the supine and standing positions were followed before, during and after irradiation for malignant tumours in 114 patients A statistically significant gradual reduction in blood pressure during the treatment period was established This was more marked in older patients and in patients with higher initial blood pressure but was not related to the region irradiated or the type of tumour treated Particularly if the patient experiences vertigo and nausea on change of position, it seems advisable to check the blood pressure during treatment

ZUSAMMENFASSUNG

Bei 114 Patienten mit malignen Tumoren wurden Blutdruck und Herzfrequenz vor und nach der Bestrahlung in Ruhe in liegender und aufrechter Lage untersucht Ein statistisch signifikanter Abfall des Blutdrucks während der Behandlungsperiode wurde festgestellt Dieser war stärker ausgeprägt bei älteren Patienten und Patienten mit einem initial hohen Blutdruck war jedoch nicht zur bestrahlten Körperregion und dem Typ des Tumors relatiert Besonders wenn bei Patienten Schwindel und Übelkeit bei Änderung der Körperlage auftritt scheint es empfehlenswert zu sein während der Behandlung den Blutdruck zu kontrollieren

RÉSUMÉ

La pression sanguine et le rythme cardiaque au repos en position couchée et en position debout ont été étudiés avant pendant et après l irradiation de tumeurs malignes chez 114

malades Les auteurs ont trouvé une réduction graduelle statistiquement significative de la pression sanguine pendant la période de traitement Elle est plus marquee chez les malades âgés et chez les malades qui avaient une pression sanguine initiale elevee mais n'est pas en rapport avec la région irradiée ni avec le type de tumeur traitée Il paraît utile de vérifier la pression sanguine pendant le traitement, en particulier si le malade eprouve des vertiges et des nausées aux changements de position

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ABSORBED DOSE IN MAMMARY RADIOGRAPHY

M KARLSSON, K NYGREN, G WICKMAN and G HETTINGER

The mammary gland is at present one of the most frequent sites of malignant tumours and mammary radiography has been suggested as a mass screening method for the early diagnosis of these tumours In order to obtain sufficiently high subject contrast and spatial resolution in the film, a low energy technique and a recording medium with high resolution are necessary This combination may result in such a high absorbed dose that the radiation hazards may be significant

In this report are presented the results of measurement made with an ionizing chamber in an alcohol–water mixture simulating breast tissue in the radiation field from a molybdenum anode at radiation qualities commonly used in mammary radio graphy

The radiation hazards are generally assumed to have a close relationship to the average absorbed dose to the organ of interest Therefore, the experimentally deter-mined exposure distributions were converted to absorbed doses, and mean values for the whole irradiated volume were calculated The values for the absorbed dose were then applied to various clinical recording systems including a film-screen system (Du Pont LoDose), an industrial film (Kodak Industrex C), a rapid processing 'mammography' film (Kodak RP/M) and xeroradiography (Xerox) A phantom was designed in order to compare the sensitivity of the different recording media at the radiation qualities giving similar image quality

Methods

The experimental set-up for the measurement of the exposure distribution in the central ray appears in Fig 1 The radiation equipment was a Philips Diagnost M

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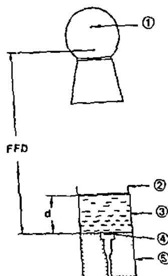


Fig. 1 Experimental set up for the measurement of exposure distribution FFD 50 cm. 1 = Molybdenum anode tube 2 = Thin bottomed lucite cylinder 3 = Phantom material 4 = Thin walled ionization chamber 5 Polystyrene block

with a molybdenum anode tube and a thin beryllium window The tube potentials used varied from 26 to 53 kV The kV settings were calibrated using the potential divider method External filtration 0 03 mm Mo was used in exposing the films and film screen combination and 0 5 mm Al for the Xerox cassettes The phantom material was a mixture of 82 % ethanol by weight and 18 % water (85 and 15 per cent by volume respectively) This composition has been reported to be a good substitute for the average breast tissue (NIEVELSTEIN 1968, JÖTTEN et coll 1974)

A thin bottomed cylindrical lucite tube 90 mm in diameter was filled to desired levels with the phantom material for the depth exposure measurements The ionization chamber was placed at a fixed distance from the tube focus with its entrance window close to the thin bottom of the cylinder The chamber itself was surrounded by polystyrene in order to obtain approximately the same scattering probability as in breast tissue The ionization chamber was especially designed for these measurements It had an entrance window of 0 2 mm graphite and an ionization volume of 0 24 cm³ The chamber was exposure-calibrated at the Standards Laboratory of the Swedish National Institute of Radiation Protection The accuracy of the calibration was estimated to be within 10 per cent of the true value The chamber response to the radiation qualities used appears in Fig 2

The conversion of exposure X to the absorbed dose in the phantom material D_{med} was performed according to

$$D_{med} = f_{med}\ X, \quad f_{med} = 0.869\ \frac{(\mu_{en}/\rho)\,\mathrm{med}}{(\mu_{en}/\rho)\,\mathrm{air}}$$

The mass energy absorption coefficients were obtained from ICRU Report No 17 (1970) In Table 1 are given the calculated values of the conversion factor f_{med} for

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ABSORBED DOSE IN MAMMARY RADIOGRAPHY

M KARLSSON, K NYGREN, G WICKMAN and G HETTINGER

The mammary gland is at present one of the most frequent sites of malignant tumours and mammary radiography has been suggested as a mass screening method for the early diagnosis of these tumours In order to obtain sufficiently high subject contrast and spatial resolution in the film, a low energy technique and a recording medium with high resolution are necessary This combination may result in such a high absorbed dose that the radiation hazards may be significant

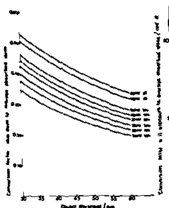
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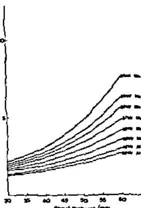


Fig 4 Fig 5

Fig. 4 Factors for the conversion of skin dose to average absorbed dose at FFD = 50 cm.

Fig. 5 Average absorbed dose normalized to the exposure at the recording media at FFD = 50 cm. To get the corresponding values in SI units Gy × (C × kg^{-1})$^{-1}$ multiply the rad × R^{-1} value with 38 8

sorbed dose along the central ray averaged from zero to the actual depth If these values are taken as the average absorbed dose for the whole breast, a slight over-estimation is generally introduced due to the inhomogeneity of the primary radiation field With the equipment used, the exposure in the central ray was approximately 10 per cent higher than the average exposure in the whole radiation field However, this over-estimation is partly compensated by the slightly higher average dose which occurs in the thinner peripheral parts of the breast

In previous reports it has been customary to present the skin dose only Factors for the conversion of skin dose to average dose at different radiation qualities and object thicknesses are given in Fig 4 In Fig. 5 the average absorbed dose normalized to the exposure at the recording medium is presented

Clinical applications If the absorbed doses to the breast for different recording media are to be compared the comparison must be made between those radiation qualities which result in similar image qualities in the different media Rough estimations of the image qualities were obtained using the slit phantom shown in Fig 6 This phantom was manufactured from a piece of polyethylene in which slits of various widths and depths were milled and the polyethylene was surrounded by water in order to simulate general tissue inhomogeneities The total slit length visible in the image of the phantom was taken as a figure of merit of the image quality The image qualities thus defined for different recording media and tube potentials are given in Fig 7

In Table 2 appears one set of radiation qualities of which the different recording media give similar image quality The table also gives the exposures required at the entrance surface to the recording medium to obtain an optical density of 1.2 on the films and optimum exposure to the Xerox cassette The films were developed in accordance with the instructions given by the manufacturers Du Pont LoDose

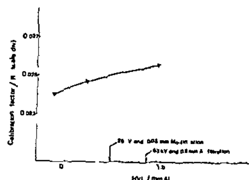


Fig 2

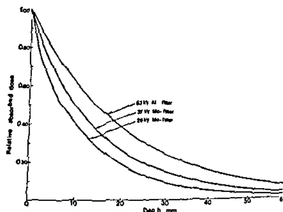


Fig 3

Fig 2 Exposure calibration of the ionization chamber To get the corresponding values in SI units $C \times kg^{-1} \times$ (scale div) $^{-1}$ multiply the R × (scale div) $^{-1}$ with $2\ 58 \times 10^{-4}$

Fig 3 Dose distribution along the central ray in the phantom material FFD = 50 cm

monoenergetic photons in the energy range 15 to 40 keV With the tube potentials applied for these measurements the spectra from a molybdenum anode are dominated by photons with energies from 10 to 25 keV (KYSER 1972) Thus an f factor of 0 59 rad R^{-1} (22 5 Gy × (C × kg $^{-1}$) $^{-1}$) was used as an approximation for all primary radiation qualities and phantom depths

Results

Depth dose distributions along the central ray for some different radiation qualities are given in Fig 3 The dose distributions are approximately valid for all possible breast thicknesses since the backscatter contribution is small and the scatter from film, screen or Xerox cassette is approximately the same as that from the breast tissue The values for the mean absorbed dose in the breast have been calculated as the ab

Table 1

Calculated f factors for the ethanol water mixture

Photon energy	f (rad/R)
15	0 59
20	0 59
30	0 59
40	0 64

To get the corresponding values in SI units Gy × (C × kg $^{-1}$) $^{-1}$ multiply the rad × R $^{-1}$ value with 38 8

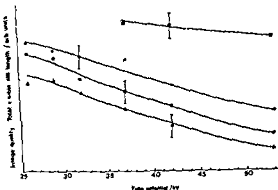


Fig 7

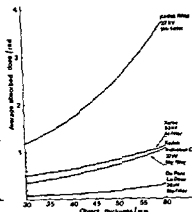


Fig 8

Fig 7 Image quality as a function of tube tension for different recording media ■ = Xerox, 0 5 mm Al filtration ★ = Kodak Industrex C, 0 03 mm Mo filtration ● = Kodak RP/M, 0 03 mm Mo-filtration ▲ Du Pont LoDose, 0 03 mm Mo-filtration

Fig 8 Average absorbed dose with different recording media at comparable image quality To get the corresponding values in SI units mGy multiply the rad value with 10

Discussion

The image quality as defined above was for all radiation qualities found to be superior in the Xerox print to that in the films However, the slitphantom favours the Xerox print as the phantom simulates discontinuously varying inhomogeneities in the object Due to the enhancement of high spatial frequencies, the Xerox image records the appearance of the phantom better than diffusely varying attenuations However, the intercomparison among the radiographic films should be relevant

The absorbed dose to the breast is strongly depending on the recording media used (Fig 8) The results show radiographic films, Kodak RP/M and Du Pont LoDose, both designed for mammary radiography to differ by more than a factor of ten in absorbed dose to the breast when the films are exposed to obtain the same average density of 1 2 and similar image quality

Other important factors which affect the absorbed dose are the film processing technique, film density, breast thickness and the choice of radiation quality There are also large individual variations in the tissue composition of the breast This is for example age dependent In general, older women have more fatty tissue than younger ones and will consequently receive lower [illegible] on the alcohol-water mixture (NIEV [illegible] made on patients indicate that the [illegible] can be accepted as a sufficiently good substitute for the average breast of older women However, if the average dose in screening is to be more established, further

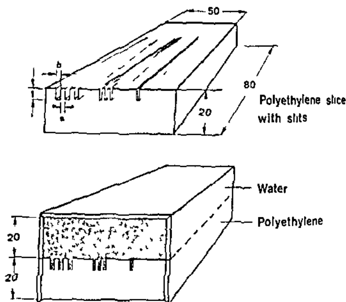


Fig 6 Slitphantom a = b = 1 0, 0 8, 0 7, 0 6, 0 5, 0 4, 0 3 and 0 25 mm, respectively All measures in mm

and Kodak RP/M-films were developed for 90 seconds in a Pakorol roll developer Kodak Industrex C was developed manually for 4 minutes The chemicals used were fresh and from the same manufacturer as the actual photographic film The temperatures in the developer were controlled externally

The absorbed dose average in the phantom material at different thicknesses (Fig 8) were calculated from the exposures required at the different radiation qualities to give similar image qualities

Table 2

The exposure required to produce a density of 1 2 on the films or optimum blackening of the Xerox print The tube potentials at which the different recording media gave similar image quality are underlined

Parameters		Xerox (mR)	Du Pont (mR)	Industrex C (mR)	RP/M2 (mR)
kV	Filter				
53	Al	380			
42	Al	390			
53	Mo		23 0	175	510
42	Mo		25 0	190	560
37	Mo		27 0	210	610
32	Mo		28 5	230	670
29	Mo		30 0	250	740
26	Mo		32 0	280	810

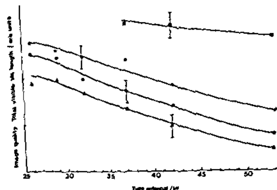


Fig 7

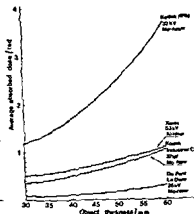


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Other important factors which affect the absorbed dose are the film processing technique film density, breast thickness and the choice of radiation quality There are also large individual variations in the tissue composition of the breast This is for example age dependent In general, older women have more fatty tissue than younger ones and will consequently receive lower absorbed doses Previous reports on the alcohol-water mixture (NIEVELSTEIN, JÖTTEN et coll) as well as measurements made on patients indicate that the alcohol-water mixture used in this investigation can be accepted as a sufficiently good substitute for the average breast of older women However, if the average dose in screening is to be more established, further

measurements on phantom materials must be made with other ethanol-water mixtures The determinations of the compositions of such mixtures require further measurements on large groups of women of different ages

SUMMARY

By exposure measurements in an alcohol-water mixture simulating breast tissue, the absorbed dose, and dose distribution in the breast at the radiation qualities commonly used in mammary radiography have been calculated The absorbed doses for different recording media have been compared at those radiation qualities which result in similar image qualities in the different recording media

ZUSAMMENFASSUNG

Durch Exponierungsmessungen in einer Alkohol-Wasser Mischung, die das Brustgewebe simuliert, wurde die absorbierte Dosis und die Dosisverteilung in der Brust fur die gewohnlich verwendeten Strahlenqualitäten bei der Brustrontgenuntersuchung berechnet Die absorbierten Dosen fur verschiedene registrierende Media wurden bei solchen Strahlenqualitäten verglichen, die zu gleichen Bildqualitaten fur die verschiedenen registrierenden Medien fuhren

RÉSUMÉ

Par des mesures de dose d'exposition dans un mélange d'alcool et d'eau simulant le tissu mammaire les auteurs ont calculé la dose absorbée et la distribution de dose dans le sein pour des qualités de rayonnement habituellement utilisées en radiographie mammaire Les doses absorbées pour différents moyens d'enregistrement d'image ont été comparées pour des qualités de rayonnement donnant une qualité d'image similaire avec ces différents moyens d'enregistrement

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ATTENUATION EQUALIZING FILTER IN DIAGNOSTIC RADIOGRAPHY

Advantages calculated by a Monte Carlo technique

L KUSOFFSKY, C A CARLSSON and P EDHOLM

An attenuation equalizing filter, even called a dodger, is intended to compensate for large attenuation differences in an object, e g the skull, the trunk or the knee joint, in radiography or fluoroscopy (EDHOLM & JACOBSON 1971) The skull equalizer is an ellipsoidal excavation in an aluminium block which is placed near the roentgen tube and positioned with respect to the skull by optical means The equalizer attenuates the radiation penetrating the thinner part of the skull

The attenuation equalizer affects the image quality in three different ways (1) all parts of the object are exposed to give an image within the useful range of the detector (2) the ratio of primary to total radiation is changed, and (3) the spectrum of the radiation received by the patient is changed

Less absorbed energy (energy imparted) is also administered to the patient

To assess quantitatively how the image quality is influenced by the attenuation equalizing filter (equalizer) calculations of the scattered radiation to the detector and the absorbed energy in the object have been carried out by a Monte Carlo method using mathematical models of the radiation, the equalizing filter, the skull and the detector The primary radiation to the detector and the contrast given by small details have been treated analytically

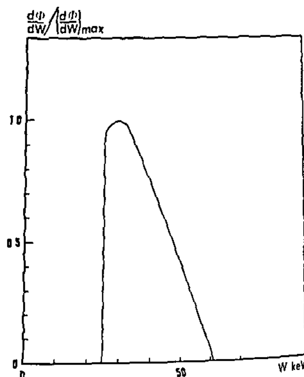


Fig 1 The roentgen spectrum used in the calculations

The mathematical model

The radiation was considered to be isotropic The film-focus distance was 90 cm

The spectrum of the radiation is based on measurements with a roentgen generator fed by 60 kV constant potential (MIKA & REISS 1969) The 60 kV spectrum appears in Fig 1

A cut-off was made at 25 keV and all photons with lower energy were considered to be stopped in the equalizing filter when this technique was used and in the ordinary aluminium filter when no equalizer was used In another calculation, the incident radiation was chosen to be mono energetic 60 keV photons The geometry was identical as with the spectrum

The equalizing filter was taken as being 17 mm thick at the periphery, to be made of aluminium and with an ellipsoidal excavation corresponding to the skull In the centre no material was present

A water-filled sphere, 170 mm in diameter, placed in contact with a detector, was used as a skull phantom For some calculations, the sphere was considered to contain small holes 2 mm deep in the direction of the rays and with negligible cross-sectional area

The detector was assumed to be a screen-film combination with a given characteristic curve The results were calculated for totally absorbing as well as for partially absorbing screens Finally the influence of a secondary radiation grid on the results was calculated

The Monte Carlo technique

A review of the application of the Monte Carlo technique to photon penetration is given by FANO et coll (1959), where the mathematical details appear

The Monte Carlo technique is based on deriving a random variable x from a differential distribution f(x) by setting

$$x = F_{-1}(\text{RANF}) \tag{1}$$

where F_{-1} is the inverse of the integral distribution corresponding to f(x) and RANF is a random number generated by the computer

A large number of photon tracks were followed from the source through the object to the detector Each photon track was associated with a weight factor which made it possible to use 'analytical averaging', that is, replacing a random variable by its expectation value, and 'importance sampling', that is, abandoning direct simulation and instead using false' distributions and correcting the results by change of the weight factor

This made the statistical fluctuations of the results much smaller for a given number of incident photons because more photons reached the detector

The program was written in FORTRAN V and is rather general because it is intended for use in different fields of radiography

Importance sampling was used for the input directions to get more photon tracks in the centre where the area per unit radial distance in the detector plane is small and for the input energy to get more high energy photons

Attenuation coefficients were calculated from eqs 2 and 3 for the actual photon track each time the photon energy W was changed

Only Compton scattering and photoelectric absorption were considered For Compton scattering the coefficient σ (cm^{-1}) for water was calculated from the expression

$$\sigma = aW^2 + bW + c \tag{2}$$

where

$$a = 1\,2 \times 10^{-6}\ keV^{-2}\ cm^{-1}$$

$$b = -0\,6 \times 10^{-3}\ keV^{-1}\ cm^{-1}$$

$$c = 0\,217\ cm^{-1}$$

This gives values with less than 0 5% deviation between 30 and 200 keV when compared with tabulated values (HUBBELL 1969)

For the photoelectric coefficient, τ,

$$\tau = \exp(8\,973 - 3\,2179\ {}^{e}\log W), \tag{3}$$

$$(W \text{ in keV}, \tau\ cm^{-1})$$

giving deviations from the tabulated values for water of less than 1 4% between 10 and 200 keV

Coherent scattering has been neglected which results in an under-estimate of the scattered radiation which is partially compensated for by the neglect of the reduced incoherent scattering caused by the binding energy of the orbital electrons

For the path length between different interaction sites, the true physical probability distribution was used For photoelectric absorption analytical averaging was used so that every interaction between a photon and the object was a Compton scattering event Tests were also made to check that the photon was still in the object For the Compton scattering angle, a 'false' distribution was used which exaggerated the scatter towards the detector, while the correct probability which must be known to calculate the new weight factor was taken from the Klein Nishina formula The photon then made a new 'flight' with a new weight, a new direction and a new energy When the energy of the photon dropped below 22 keV the track was terminated and the photon was considered to be absorbed

Photons which hit the detector within the image of the object made by the primary radiation were filed according to their energy, their position, their angle of incidence on the detector and as to whether or not they had been scattered

The primary radiation arriving at the detector was also calculated by another program using the ordinary attentuation formula These latter results constituted a test of the Monte Carlo method but their main objective was to get values without statistical fluctuations

Four situations were examined Polyenergetic radiation (60 kV) and monoenergetic radiation (60 keV), in both cases with and without the equalizing filter

In the calculation of the image contrast caused by the 2 mm deep holes in the sphere only the decreased attenuation of the primary photons was considered the reduction in the scattered radiation being neglected

Experimental test of calculations

The results from the calculations with the 60 keV photons were compared with data from an experiment in which the details of the calculations were simulated as closely as possible

The radiation source was a filtered ^{241}Am source, 3 mm in diameter, giving essentially 59 6 keV photons The equalizing filter was machined from aluminium with the same dimension as used in the calculations The skull phantom was a spherical water filled football bladder, 170 mm in diameter A Na I scintillation detector was used together with a multichannel analyzer

The focus detector distance was 900 mm and the equalizing filter was placed so near the radiation source that the influence of scattered radiation from the filter on the measurements was negligible The detector was collimated with a flat lead collimator of an area of 1 cm² and placed just under the football bladder Measurements were made at different distances from the centre In all the measurements the detector and collimator surfaces were perpendicular to the central ray, i e , the plane number

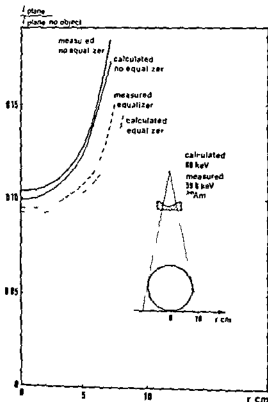


Fig 2. Calculated and measured plane number fluences for 60 keV photons

fluence, defined in eq 4, was measured The resulting plane number fluences from the measurements and the calculations appear in Fig 2

By the plane number fluence, ϕ_{bl}, it is meant

$$\phi_{bl} = \iint \frac{c^2\phi}{cWc\Omega} \vec{\Omega} \cdot \vec{a}\, dW\, d\Omega \tag{4}$$

where $\vec{\Omega}$ is a unit vector giving the direction of the photons, $\vec{a}$ is a unit vector normal to the entrance plane of the detector, ϕ is the fluence, W the photon energy and Ω is a solid angle

The Monte Carlo technique was also tested by simulating some experiments on backscattering from water made by BJÄRNGARD & HETTINGER (1961). The agreement was within the statistical limits

Results

The computer program was run with the 60 kV spectrum Calculations were made with and without an equalizing filter In the Monte Carlo procedure 160 000 photon histories were examined

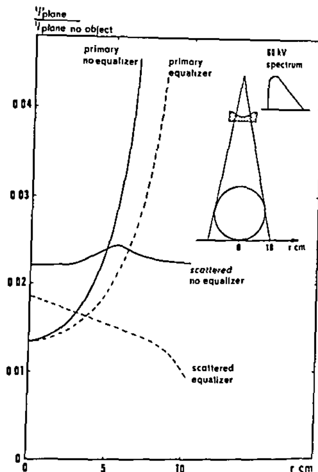


Fig 3 Plane energy fluences in the detector plane with and without the use of equalizer

The plane energy fluences ψ_{pl} as a function of the distance from the centre in the detector plane are given in Fig 3 The plane energy fluence ψ_{pl} equals the energy imparted per unit area for a totally absorbing detector and is defined similarly to ϕ_{pl}

$$\psi_{pl} = \iint \frac{\partial^2 \phi}{\partial W \partial \Omega} \, W \vec{\Omega} \ \vec{a} \, dW \, d\Omega \tag{5}$$

To illustrate how the contrast for small details is enhanced by the equalizer, a detector with a response approximating to that of a film screen combination was simulated for the following calculations The detector was defined by

$$D = \gamma(E) \ {}^{10}\log E + D_0 \tag{6}$$

which quantity is plotted in Fig 4

E *is the energy imparted per unit area in the detector* $\gamma(E)$ *is given by the slope* (eq 7) and D is the optical density of the film D_0 is the optical density for an unirradiated film

$$\gamma(E) = \frac{dD}{d({}^{10}\log E)} \tag{7}$$

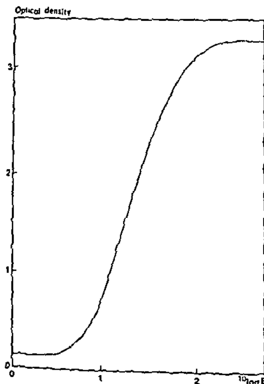


Fig 4 The optical density D for the hypothetical detector as a function of the energy imparted per unit area

If the image contrast is defined as the difference in optical density, ΔD, a contrast enhancement function can be defined as

$$K = \frac{(\Delta D')_{eq}}{(\Delta D)_{no\ eq}} = \frac{(\gamma(E' + \Delta E')\ {}^{10}\log(E' + \Delta E') - \gamma(E')\,{}^{10}\log E')_{eq}}{(\gamma(E + \Delta E)\ {}^{10}\log(E + \Delta E) - \gamma(E)\,{}^{10}\log E)_{no\ eq}} \tag{8}$$

ΔE is the difference in E due to the small holes, the index eq denotes the equalizing filter and the prims denote values obtained with the equalizer

The results calculated for the sphere with holes with and without an equalizer are presented in Fig 5 The detector is assumed to be totally absorbing The holes cause increased optical densities indicated by bars in Fig 5 The contrast enhancement factor K(r) is the ratio between these bars, with and without an equalizer, as a function of the distance, r, from the image centre

For the case with small holes in the water sphere, the increased energy imparted per unit area ΔE, caused by a hole is small compared to E, the energy imparted per unit area without a hole

$$\Delta E < E$$

and, hence, as a result (9)

$$^{e}\log\left(1 + \frac{\Delta E}{E}\right) \simeq \frac{\Delta E}{E} \tag{10}$$

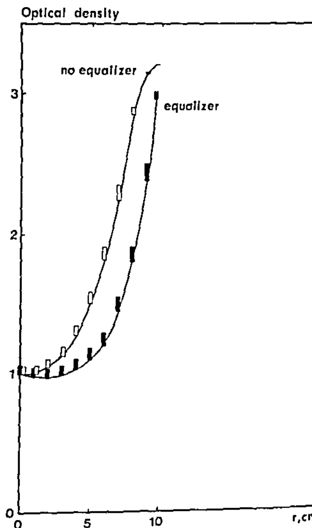


Fig. 5. Variation of optical density as function of the distance from the centre of a water sphere with 2 mm deep holes. The bars illustrate the contrast caused by the holes.

Differentiation of eq. 6 gives

$$dD = \left\{\gamma(E)\ 0.43\frac{1}{E} + \frac{d\gamma(E)}{dE}\ 0.43\,{}^{e}\log E\right\} dE \tag{11}$$

If

$$\frac{d\gamma}{dE} < \frac{1}{E}\ \frac{\gamma(\Gamma)}{{}^{e}\log E} \tag{12}$$

it follows that

$$\gamma(E) \simeq \gamma(E + \Delta E) \tag{13}$$

Eq. 7 can now be simplified as follows

$$K = \frac{(\Delta D')_{eq}}{(\Delta D)_{no\ eq}} = \frac{\gamma(E')\,{}^{10}\log\dfrac{E' + \Delta E'}{E'}}{\gamma(E)\,{}^{10}\log\dfrac{E + \Delta E}{E}} \simeq \frac{\gamma(E')\,\dfrac{\Delta E'}{E'}}{\gamma(E)\,\dfrac{\Delta E}{E}} \tag{14}$$

E is composed of contributions from both primary, E_p, and scattered radiation, E_s,

$$E = E_p + S_s \tag{15}$$

Eq 14 can be rewritten

$$K = \frac{\gamma(E')}{\gamma(E)} \; \frac{\frac{E'_p}{E'}}{\frac{E_p}{E}} \; \frac{\frac{\Delta E'}{E_p}}{\frac{\Delta E}{E_p}} = K_1 \; K_2 \; K_3 \tag{16}$$

The three components of the contrast enhancement function can be discussed separately

$$K_1 = \frac{\gamma(E')_{eq}}{\gamma(E)_{no\ eq}} \tag{17}$$

expresses the contrast change caused by the difference in detector characteristics at the different energies absorbed

$$K_2 = \frac{(E_p/E')_{eq}}{(E_p/E)_{no\ eq}} \tag{18}$$

expresses the influence on the contrast relation caused by different ratios of primary to total radiation

$$K_3 = \frac{(\Delta E'/E_p)_{eq}}{(\Delta E/E_p)_{no\ eq}} \tag{19}$$

expresses how the transparency of the object is changed by different primary filtration

These three ratios correspond to the three image quality factors discussed in the introduction

The results are first discussed for the case of a totally absorbing detector, that is

$$E_p = \psi_{pl\ p}, \Delta E = \Delta\psi_{pl} \quad \text{and} \quad E_s = \psi_{pl\ s} \tag{20}$$

The contrast enhancement factors are given in Fig 6 for the case appearing in Fig 5, that is, with the same optical density on the two films at the centre of the water sphere

In diagnostic radiography the detector does not absorb all the incident energy Furthermore the number of photons incident on the detector as well as their energy and angular distributions are changed both by the interposition of a grid and of an object-detector distance

An attempt to calculate a realistic case requires eqs 21 to 23

$$E_p = \int 0\,85 \;\; b(W) \frac{d\psi_{pl\ p}}{dW} dW \tag{21}$$

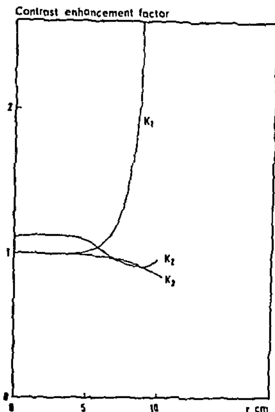


Fig 6

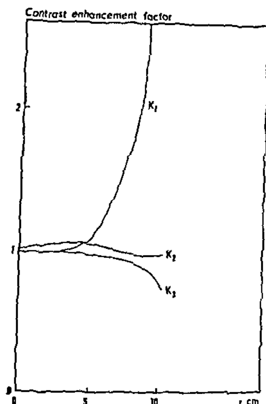


Fig 7

Fig 6 Contrast enhancement factors along a radius for a *totally absorbing film screen combination*

Fig 7 Contrast enhancement factors for a detector absorbing an energy-dependent fraction of the photons used *together with a grid*

$$\Delta E = \int 0.85 \;\; b(W) \frac{d\Delta\psi_{p)}}{dW} dW \tag{22}$$

$$E_s = \int a(W) \;\; c(W) \frac{d\psi_{p) s}}{dW} dW \tag{23}$$

Here, a(W), the amount of the scattered radiation not absorbed by a hypothetical grid, *is calculated* by the Monte Carlo code The number of primary photons is *assumed to be decreased to 85 % by the grid* b(W) *is the fraction of* the energy of the photons absorbed in a detector consisting of two $CaWO_4$-screens This function b(W) is given by TER-POGOSSIAN (1967) b(W) is given for perpendicular incidence and is applicable for the primary radiation For the scattered radiation another absorbed fraction c(W) is used in eq 23 due to the angular distribution For simplicity, c(W) has been set equal to b(W) though this is correct only for scattered radiation with nearly perpendicular incidence The results in Fig 7 correspond to a detector which absorbs an energy-dependent fraction of the incident energy used together with a grid of ratio 8

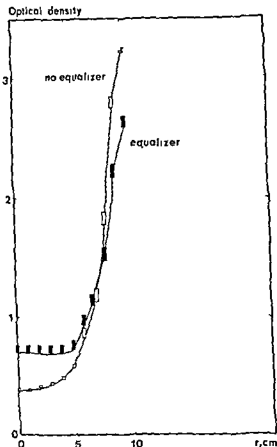


Fig 8 Optical density for an exposure of a water sphere with 2 mm deep holes The bars illustrate the contrast caused by the holes The film obtained with an equalizing filter was exposed by a factor 1 6 more than the other

The change in the energy absorbed in the object (energy imparted, integral dose) when using an equalizer compared to the conventional technique is dependent on how much the charge passing the roentgen tube is changed This is determined by the exposure (mAs-setting)

The reduction in absorbed energy for the different cases is given in the Table Exposure according to case c) or d) is often made in practice to give an image with about the same optical density averaged over the whole image

Figs 5 to 7 are calculated using case b) (Table), that is, with the same optical density in the centre with and without the equalizing filter

An increased exposure ratio, cases c) and d) (Table), does not influence the factors K_2 and K_3 of eq 16 The factor K_1, however, depends on both the exposure ratio and the average optical density level chosen

Fig 8 illustrates as an example the optical densities as a function of the radius

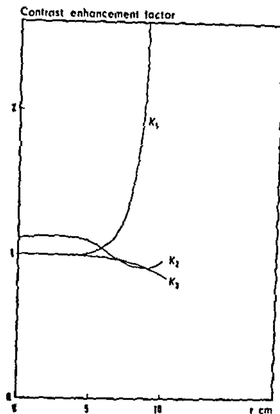


Fig 6

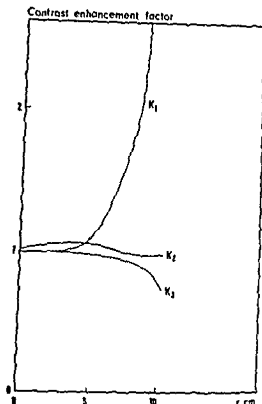


Fig 7

Fig 6 Contrast enhancement factors along a radius for a totally absorbing film screen combination
Fig 7 Contrast enhancement factors for a detector absorbing an energy-dependent fraction of the photons used together with a grid

$$\Delta E = \int 0\,85 \quad b(W) \frac{d\Delta\psi_{pl}}{dW} dW \tag{22}$$

$$E_s - \int a(W) \quad c(W) \frac{d\psi_{pl\,s}}{dW} dW \tag{23}$$

Here, a(W), the amount of the scattered radiation not absorbed by a hypothetical grid, is calculated by the Monte Carlo code The number of primary photons is assumed to be decreased to 85 % by the grid b(W) is the fraction of the energy of the photons absorbed in a detector consisting of two $CaWO_4$-screens This function b(W) is given by TER-POGOSSIAN (1967) b(W) is given for perpendicular incidence and is applicable for the primary radiation For the scattered radiation another absorbed fraction c(W) is used in eq 23 due to the angular distribution For simplicity, c(W) has been set equal to b(W) though this is correct only for scattered radiation with nearly perpendicular incidence The results in Fig 7 correspond to a detector which absorbs an energy-dependent fraction of the incident energy used together with a grid of ratio 8

primary to total radiation (factor K_2 in eqs 16 and 18) (b) A hardening of the primary spectrum resulting in lower contrast (factor K_3 in eqs 16 and 19) The slight disadvantages caused by the factors K_2 and K_3 at the peripheral parts of the skull are almost negligible compared with the great advantage caused by factor K_1 (c) A further disadvantage is the necessary increase in exposure time to give the same average optical density of the film

The last disadvantage (c) classes the equalizer method together with many other methods of increased image quality by reducing scattered radiation, e g use of secondary radiation grids increased distance between object and detector as well as increased collimation of the beam

The question as to how far the equalizing effect can be utilized cannot generally be answered In most cases the equalizer should not attenuate the primary radiation more than that all the interesting parts of the object are imaged within the useful range of the detector

SUMMARY

The value of an attenuation equalizing filter (equalizer) has been examined by calculation using a Monte Carlo technique The contrast enhancement caused by the equalizer is the net result of three factors (1) The first factor arises from the contrast change caused by the difference in detector characteristics at the different energies absorbed in the detector with and without equalizer (2) The second factor is due to the contrast change caused by the different ratios of primary to total radiation reaching the detector (3) Finally the third factor describes how the transparency of the object is changed by the different primary filtration with equalizer An example is given of the reduction in radiation energy absorbed by the patient and the question of how far the attenuation equalization can be driven is discussed

ZUSAMMENFASSUNG

Der Wert von einem Verdunnungsfilte [illegible]
Verwendung der Monte Carlo Technik [illegible]
[illegible] hervorgerufen durch die verschiedenen Verhältnisse der primaren zur gesamten Strahlung, die den Detektor erreicht, verursacht 3 Schliesslich beschreibt der dritte Faktor [illegible]
durch die verschiedene Primärfiltneru [illegible]
spiel für die Verminderung in der Str [illegible]
geben und die Frage diskutiert wie w [illegible] ungsausgleich betrieben werden kann

RÉSUMÉ

Les auteurs ont examiné par des calculs utilisant une technique de Monte-Carlo l intérêt d un filtre égalisant l atténuation (égalisateur) L'amélioration du contraste obtenu grâce

Table

Reduction in absorbed energy

Case	Exposure change by a factor	(Absorbed energy)$_{eq}$ / (Absorbed energy)$_{no\ eq}$
a) No exposure change	1 0	0 52
b) Exposure to give the same absorbed energy per unit area in the centre of the detector	1 11	0 58
c) Increase by one mAs step (26 %)	1 26	0 66
d) A change by two mAs steps	1 60	0 83

from the image centre and the contrast given by the small holes in the sphere (cf Fig 5)

Discussion

Many parameters (kV, skull phantom, material and thickness of the equalizer, detector characteristics, optical density levels, etc) have been chosen in a rather arbitrary way Nevertheless, the results give a rough understanding of the effects to be expected when using an equalizer in skull examinations

For instance, a skull with bone of varying thickness results in an image with an increased range of optical densities compared with that of the water sphere The value of an equalizer in skull examinations is then even higher than demonstrated in the present report

The arbitrary terminating of a history at 22 keV in the Monte Carlo program is not quite correct The number of photons with energy below 22 keV is, however, low, as only those generated near the phantom exit surface penetrate to the detector Furthermore, as the detectors absorb all or most of the incident radiation energy low energy photons produce little effect in the detector

Conclusion

The equalizer is valuable in skull examinations when film is used together with intensifying screens as detectors because of (1) A diminished range of optical densities in the film which brings thin, peripheral parts of the skull within the useful range of the detector for a chosen optical density at the thick, central part (factor K_1 in eqs 16 and 17) (2) A lower contribution of scattered radiation to the central parts of the image (factor K_2 in eqs 16 and 17) (3) Lower radiation doses to the patient

A slight disadvantage arises from the filtration of informative primary radiation at peripheral parts of the skull This results in (a) An impaired relationship between

primary to total radiation (factor K_2 in eqs 16 and 18) (b) A hardening of the primary spectrum resulting in lower contrast (factor K_3 in eqs 16 and 19) The slight disadvantages caused by the factors K_2 and K_3 at the peripheral parts of the skull are almost negligible compared with the great advantage caused by factor K_1 (c) A further disadvantage is the necessary increase in exposure time to give the same average optical density of the film

The last disadvantage (c) classes the equalizer method together with many other methods of increased image quality by reducing scattered radiation, e g use of secondary radiation grids, increased distance between object and detector as well as increased collimation of the beam

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ZUSAMMENFASSUNG

Der Wert von einem Verd [illegible] Verv [illegible] den [illegible] dem [illegible] durch den Unterschied in den Detektorcharakteristika für die verschiedenen absorbierten Energien im Detektor mit und ohne Ausgleicher, her 2 Der zweite Faktor wird durch den Kontrastwechsel hervorgerufen durch die verschiedenen Verhältnisse der primären zur gesamten Strahlung, die den Detektor erreicht verursacht 3 Schliesslich beschreibt der dritte Faktor [illegible] durch die verschiedene Primärfilteru [illegible] spiel für die Verminderung in der Str[illegible] geben und die Frage diskutiert wie we[illegible] [illegible]sausgleich betrieben werden kann

RÉSUMÉ

Les auteurs ont examiné par des calculs utilisant une technique de Monte-Carlo l intéret d un filtre égalisant l atténuation (égalisateur) L amélioration du contraste obtenu grace

à l égalisateur est le résultat net de 3 facteurs (1) Le premier facteur provient de la modification du contraste résultant de la différence des caractéristiques du détecteur aux différentes énergies absorbées dans le détecteur avec et sans égalisateur (2) Le second facteur est dû à la modification de contraste causée par les rapports différents du rayonnement primaire au rayonnement total atteignant le détecteur (3) *Enfin le troisième facteur tient* compte de la modification de transparence de l objet par filtration différente du rayonnement primaire avec l égalisatuer Les auteurs donnent un exemple de la réduction d énergie de rad ations absorbées par le malade et examinent jusqu à quel point on peut pousser l égalisation d atténuation

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UPTAKE AND RETENTION OF ^{133}Ba AND ^{140}Ba-^{140}La IN MOUSE TISSUES

L DENCKER, A NILSSON, C RÖNNBÄCK and G WALINDER

Among the fission products found in a reactor and in nuclear weapons are several isotopes of barium Of these, ^{140}Ba with a fission yield of 6 3 per cent and a half-life of 12 8 days (Radiological Health Handbook, 1970), seems to constitute an initial biologic hazard connected with nuclear fission The metabolism of barium isotopes has been investigated by impulse technique in several works (STATHER 1972, 1974, MOSKALEV 1961, LINIECKI & KARNIEWICZ 1971, CUDDIHY & GRIFFITH 1970, 1972) and it is known that barium accumulates mainly in the skeleton In spite of the close relationship between barium and strontium, barium has been found to accumulate in high concentrations in pigmented areas of the mouse eye (GARNER 1959, SIMONOVIC & PIRIE 1963) whereas strontium is not found autoradiographically in the eye (NILSSON & ULLBERG 1962) Radium, also an alcaline earth metal has, however, been found in the melanocytes of the eye (TAYLOR et coll 1964) The precise localisation of barium seems to be a knowledge of great value for evaluating the

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pathologic effects of barium isotopes Since ^{133}Ba is short-lived it will also offer a good opportunity for evaluating the carcinogenicity and pathology after a relatively short initial irradiation (up to 70 days) as compared to nuclides giving a life-long irradiation Probably valuable information could be obtained about the 'wasted irradiation', the role of which for nuclides with a very long physical half-life is debated and not fully understood The knowledge of pathologic changes caused by barium nuclides is sparse and emanates mainly from STRELTSOVA & MOSKALEV (1961), who initially found agranulocytosis, anemia, bleedings and a reduction in spermatogenesis The most obvious late effects were chondrosarcomas of the skeleton, leukaemia and papillomas of the urinary bladder

The purpose of this communication is to report the localisation of ^{133}Ba as recorded by whole body autoradiography in pigmented as well as in non-pigmented mice and to measure the concentrations of ^{140}Ba and ^{140}La by two-channel scintillation technique and to calculate the radiation doses in the skeleton and in the eyes after injections of the two latter nuclides in equilibrium

Material and Methods

Animal material Pigmented (CBA) as well as albino (NMRI) mice were used, males weighing 25 to 30 g and females about 40 g, being in late gestation The animals were kept on a complete pellet diet (AB Ewos, Sweden) at a room temperature of 25°C and had free access to water Male and female mice were mated overnight The day a mouse had a vaginal plug was considered as day 1 of pregnancy

Whole body autoradiography was performed according to a method described previously (ULLBERG 1954, 1958) $^{133}BaCl_2$ with specific activity 292 3 MBq/mg (7 9 mCi/mg), dissolved in 0 5-N HCl (obtained from the Radiochemical Centre, Amersham, England) was injected intravenously in a tail vein, each animal receiving 63 μg Ba per kg body weight, containing 18 5 MBq (500 μCi) ^{133}Ba Male pigmented mice were killed by chloroform anaesthesia 20 minutes, 4 hours and 4, 16 and 32 days after injection Female pigmented mice were killed at 1, 4 and 24 hours after injection on the 18th day of gestation and 6 days after injection on the 13th day of gestation Female albino mice in late gestation were killed at 1 and 48 hours after injection Immediately after death the animals were embedded in a mixture of carboxymethyl cellulose and water, and immersed in n hexane, cooled to −78°C with solid carbon dioxide Sagittal 20 μm and 60 μm sections through the frozen animal were cut on tape (No 810, Minnesota Mining and Manufacturing Co , U S A) in a microtome at −15°C, and dried at this temperature The dried sections were allowed slowly to attain room temperature and were pressed against films (Crystallex, Kodak) The time of exposure (at −15 C) ranged from 3 to 14 days After separation of the films from the sections, the films were developed and selected sections were stained with hematoxylin and eosin or alizarinsulfonic acid, and mounted under cover glass in Euparal (Flatters & Garnett Ltd , Manchester, England)

Impulse counting technique ^{140}Ba in equilibrium with ^{140}La was obtained from the Radiochemical Centre, Amersham, England. The measurements were carried out with a two-channel scaler (Picker Twinscale II). Due to the complex decay scheme of ^{140}Ba and ^{140}La the measurements of the γ spectrum could only give fairly broad energy 'peaks' with maximum values around 480 keV and 850 keV, respectively, when the 'window-width' was 20 keV. The determination of activities was always made simultaneously in the 480 keV-channel and the 850 keV-channel. The higher of the two energy channels records only radiation from ^{140}La whereas the 480 keV-channel records contributions from ^{140}La as well as from ^{140}Ba.

The number of counts per minute in the 480 keV-channel, N (480), can be expressed by the formula

$$N(480) = \alpha A_0(\mathrm{Ba})\, e^{-\lambda_1 t} + \beta A_0(\mathrm{La})\, e^{-\lambda_2 t} + \beta A_0(\mathrm{Ba}) \frac{\lambda_2}{\lambda_2 - \lambda_1} (e^{-\lambda_1 t} - e^{-\lambda_2 t})$$

where $A_0(\mathrm{Ba})$ and $A_0(\mathrm{La})$ are the initial activities of ^{140}Ba and ^{140}La respectively and α and β the corresponding ratios between CPM and the activities of the two nuclides. The two parameters, λ_1 and λ_2 are the decay constants for ^{140}Ba and ^{140}La respectively.

In a similar way the N(850) can be given as

$$N(850) = \gamma A_0(\mathrm{La})\, e^{-\lambda_2 t} + \gamma A_0(\mathrm{Ba}) \frac{\lambda_2}{\lambda_2 - \lambda_1} (e^{-\lambda_1 t} - e^{-\lambda_2 t})$$

When the two nuclides were in equilibrium the N(480)/N(850) ratio was found to be 2.77. By precipitating ^{140}Ba by H_2SO_4 (after the addition of inactive $Ba(NO_3)_2$ and $La(NO_3)_3$) it was possible to obtain a pure ^{140}La solution, giving a N(480)/N(850) ratio of 1.96. Since $\lambda_2/(\lambda_2 - \lambda_1) = 1.15$ we have for the ^{140}Ba$-^{140}$La decay at equilibrium

$$\frac{2.77 \cdot 1.15\,\beta}{\alpha + 1.15\,\beta} = \frac{\beta}{\gamma} = 1.96, \text{ and thus } \frac{\beta}{\alpha} = 2.1$$

By measuring the samples at various times after the death of the animals and by comparison with standard solutions it was possible to determine the parameters and $A_0(\mathrm{Ba})$ and $A_0(\mathrm{La})$.

Results

Autoradiography

General observations

Following administration of $^{133}BaCl_2$ activity was rapidly taken up by various tissues. [illegible] activity [illegible] contain [illegible] (e.g. the eye and the hair follicles). These tissues retained activity even at the longest survival time. In other tissues a rather

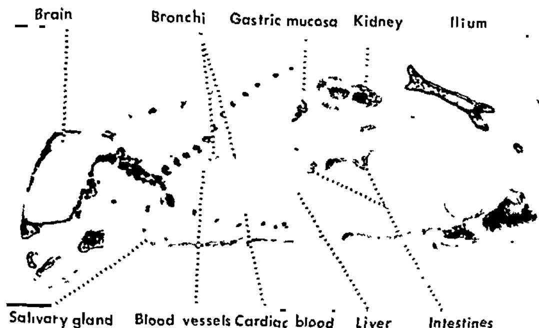


Fig 1 Whole body autoradiography of a male pigmented mouse injected with $^{133}BaCl_2$ 20 min before death High accumulation particularly in the skeleton, but also in the salivary gland, gastric mucosa, intestinal villi, kidney, bronchial walls and blood vessels Moderate uptake in the blood and lung tissues

rapid clearance of the isotope occurred. Four days after the injection, activity was found (in addition to the bone, cartilage and melanin) only in the intestinal content and the urinary tract—indicating excretion of the isotope Also 32 days after the injection, a small amount was present in these organs

The circulatory system

The initial concentration of the isotope in the blood was rather high Also 4 hours after the injection, activity was present in the blood in concentrations higher than that in the liver and muscular tissues At short survival time (up to 1 hour) a moderate uptake was seen in the walls of the large vessels (Fig 1) The myocardium had a low content throughout the entire observation period

Calcified tissues

In all bones of the body the isotope accumulated rapidly In the long bones and vertebrae, at short time intervals, the accumulation in the epiphyseal region was predominant with a somewhat lower concentration in the periosteum and endosteum of the diaphysis (Fig 2) At the longest survival times, however, the initial relations had changed In the long bones the activity in the diaphysis dominated and the relations between the periosteum and endosteum differed from one region of a particular bone to another The epiphyseal regions had a much lower concentration In the vertebrae, however, the accumulation in the epiphyseal growth cartilage was still greater or was comparable to that in the diaphyseal areas

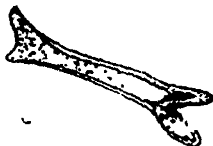


Fig 2 Detail of Fig 1, ilium High accumulation especially in the epiphyseal growth cartilage and also in the periosteum and endosteum

Skull An accumulation similar to that of the vertebrae was found in the bones of the skull base The membranous bones of the skull had a relatively high initial uptake, which then successively decreased—being rather low 32 days after the injection

Teeth The dentine had an early accumulation higher than that of the surrounding bone A similar relationship was found between dentine and bone 6 days after injection but at 32 days the activity of the dentine had decreased considerably

The cartilage At short time intervals a high accumulation of the isotope was present in the cartilage of the articular surfaces and the tracheal rings, while the concentration in the cartilage of the external ear seemed to be lower, possibly depending on the delicacy of the structure After 32 days activity was still retained in the articular and tracheal cartilage but the former cartilage seemed to have lost most of its activity

The eye

Pigmented mice At the first observation time the concentration of the isotope was already high in the uveal tract of the pigmented animals This accumulation together with that of the calcified tissues and cartilage was the highest in the body No correspondingly high activity was found in the eye of albino mice The activity was also retained in the pigmented eye at the longest survival times, when the concentration still was comparable with the average of the bone (Fig 3)

Albino mice One hour after injection, the uveal tract of albino mice had an uptake that was somewhat higher than that of other soft tissues, but not of the magnitude of that found in pigmented mice Two days after injection, the entire uveal tract except the corpus ciliare and iris had lost almost all activity (Fig 4)

The digestive system

In the salivary system the submaxillary gland accumulated activity (Fig 1) The secretory part of the gastric mucosa had a marked uptake, especially in the basal

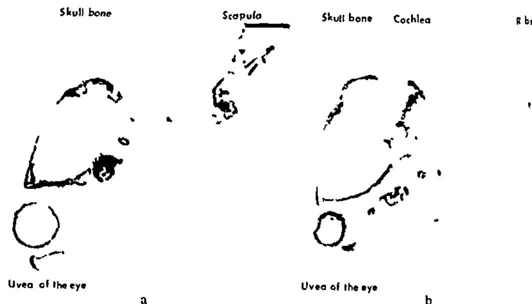


Fig 3 Detail of the autoradiography of pigmented mice a) 6 days and b) 32 days after the injection of $^{133}BaCl_2$ Only in the skeleton and in the uvea of the eye is the uptake equally high in both structures × 3

layers The mucosa of the small intestine also accumulated activity at short survival times, while at longer times the intestinal content, especially that of the large intestine had a high content After 48 hours, activity was still left in the salivary gland, the gastric mucosa and the intestinal contents Also 32 days after injection, small amounts of activity was found in the content of the large intestine

The liver and exocrine pancreas had a low concentration—lower than that of the blood Four hours after injection, the activity was hardly discernible

The respiratory organs

A faint uptake of activity occurred in the epithelium of the upper part of the respiratory apparatus In the lungs the concentration was about the same as in the blood, but the bronchi and the large bronchioli had a marked uptake (Fig 1) This accumulation persisted for 4 hours but not 24 hours after the injection

The urinary system

Already 20 minutes after injection, the whole kidney had accumulated considerable amounts of activity Especially a high content was seen in certain, not identifiable spots and streaks in the cortex, the collecting tubules of the medulla and in the pelvis Also the urinary bladder and urethra contained high amounts of the isotope After 24 hours the localised uptake in the cortex persisted and at 48 hours small amounts of activity was seen in the kidney as a whole At 16 days after the injection, activity was still found in the urinary bladder

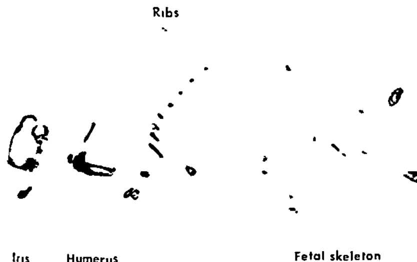


Fig 4 Whole body autoradography of an albino mouse in late gestation 2 days after the injection of $^{133}BaCl_2$ High accumulation in both the maternal and fetal skeleton No activity in the uvea of the maternal eye except for a moderate uptake in the corpus ciliare and iris

The reproductive system

Male The uptake in the testes was lower than in the blood at all observation periods No discernible uptake was found in the tubuli while the interstitial part had a low uptake giving the testis a spotty appearance (Fig 5) After 4 hours the activity in the testis was hardly visible The epididymis on the other hand had a higher concentration of activity comparable with that of the blood

In the dorsal prostate a remarkably high uptake was present at 20 minutes but not later while the concentration in the ventral prostate and the seminal vesicles did not reach that of the blood

Female All female mice were in a late stage of pregnancy The interstitial tissue of the ovaries was at the level of the blood while the corpora lutea had a lower concentration In some follicles however parts of the walls had a considerably higher concentration than the surrounding interstitium (Fig 6) This was also observed at 4 hours but at 24 hours no activity was present in the ovary

The alveolar part of the mammary gland accumulated activity and 6 days after injection it still retained moderate amounts

The endocrine organs

The hypophysis had a higher concentration of activity than the surrounding nervous system comparable with that in the blood The thyroid had an equivalent uptake and retained some of its activity 2 days after injection when the blood did

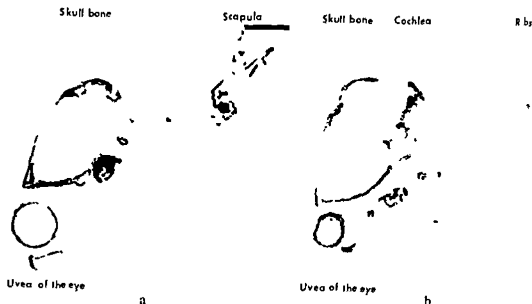


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The urinary system

Already 20 minutes after injection, the whole kidney had accumulated considerable amounts of activity Especially a high content was seen in certain, not identifiable spots and streaks in the cortex, the collecting tubules of the medulla and in the pelvis Also the urinary bladder and urethra contained high amounts of the isotope After 24 hours the localised uptake in the cortex persisted and at 48 hours small amounts of activity was seen in the kidney as a whole At 16 days after the injection, activity was still found in the urinary bladder

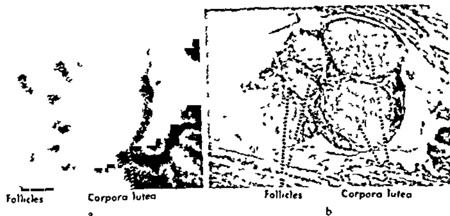


Fig 6 a) Detail of an autoradiography b) the corresponding section of a pregnant pigmented mouse 1 hour after the injection of $^{133}BaCl_2$ Slight uptake in the interstitium and the walls of the follicles, while low in the corpora lutea

sae) 32 days after injection, while no similar accumulation was found in the albino mice even at 48 hours

The placentae and fetuses

One hour after injection on the 18th day of gestation Already at this first observation time the skeleton completely dominated the distribution within the fetus The skeletal uptake, however, was considerably lower than the maternal one The cartilage had a considerable lower activity and the soft tissues were hardly discernible Within the bone, the growth zones predominated

Of the melanin-containing organs only the eye had any uptake and this was restricted to the ciliary body where the amount of melanin at this stage of development is high in comparison with the choroid (personal observation) The pelvis of the kidney and the urinary bladder also contained small amounts of activity

The placenta had an activity comparable with blood and certain spots within the placenta an uptake comparable with bone These spots were restricted to the sinus area (where the fetal vessels and the yolk sac enters the chorio-allantoic placenta) and to the decidua basalis

Four hours At this survival time the uptake in the skeleton was even more dominating compared with the soft tissues but was still lower than that in the maternal one In the soft tissues activity was seen in the lungs, especially in the bronchi, the gastric mucosa and the renal pelvis A moderate uptake was present in the cartilage and the ciliary body

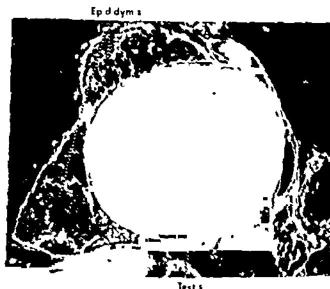


Fig. 5. Detail of an autoradiography of a male mouse 20 min after the injection of $^{133}BaCl_2$. Testis and epididymis. Low uptake in the interstitial tissues of the testis and a higher uptake in the epididymis.

not have any detectable activity. The adrenal gland had a low concentration at all survival times. In the medulla and in a thin rim of the outer cortex close to the capsula a somewhat higher uptake was present that persisted for only 1 hour after injection. In the pancreatic islands a considerable uptake was present, high at 24 hours after injection and also significant at 2 days.

The nervous system

In the plexa choroidea, activity could be seen from the first observation time and up to 4 days after injection when it was very faint. From the beginning the concentration in the central nervous system was very low but at 4 and 24 hours detectable amounts were present, especially in the brain stem and medulla oblongata. Due to cross radiation from the bone, the uptake in the spinal cord could not be evaluated.

The lymphatic system

The thymus had a low activity in all animals. Also the spleen had a low concentration, that of the red pulp being higher than that of the white. At 2 days, activity was still retained in a narrow zone of the red pulp surrounding the white pulp of the spleen. The lymph nodes did not seem to accumulate the nuclide.

The muscles and skin

At all observation periods a low concentration was present in the muscular tissues. Connective tissues had a concentration comparable with that of the blood. Also the epidermis had a moderate uptake seen also 24 hours after injection.

In the pigmented animals activity remained in the hair follicles of the nose (vibris-

Dose calculations

The dose calculations have been based on the retention curves Between day 0 and 14, the surfaces under the curves have been determined planimetrically From the second week after the injection and onwards the retention curves have been approximated by exponential curves that have been received by regression analysis of the retention figures The total dose to a certain organ can be expressed by

$$D(tot) = 0\ 512 \left[\int_0^{\infty} F_{Ba}(t)\ \bar{E}_{Ba}\ \phi_{Ba}(x)\,dt + \int_0^{\infty} F_{La}(t)\ \bar{E}_{La}\ \phi_{La}(x)\,dt \right] Gy$$

where F(t) are the retention functions (remaining activity per g organ at time t), $\bar{E}$ the mean energies and ϕ the ratio between the true mean dose in the organ 'x' and that in an infinite medium of the same density and in which the concentration of the activities of ^{140}Ba and ^{140}La are the same as those found in the organs The dose contribution from the γ radiation is negligible as compared to the β radiation and the mean energies are accordingly equal to the mean β-energies from ^{140}Ba and ^{140}La respectively The numerical values of the mean β-energies ($\bar{E}_{Ba} = 0\ 282$ MeV and $\bar{E}_{La} = 0\ 490$) have been derived from Radiological Health Handbook (1970)

The ϕ parameters are unknown The absorbed β-energy from ^{90}Sr-^{90}Y is 32 per cent (PARMLEY et coll 1962) The corresponding figure for ^{140}Ba-^{140}La should be around 45 per cent if the activity distribution can be regarded as equal for the two nuclide systems This might be approximately true for the bone tissue but certainly not for the eyes The micro distribution of the dose in bones is uncertain for ^{90}Sr and ^{90}Y and unknown for ^{140}Ba and ^{140}La

The injection of 37 kBq (1 μCi) ^{140}Ba in equilibrium with ^{140}La would give the following doses

Sternum 4 9 $\phi_{Ba}(S) + 9\ 2\ \phi_{La}(S) = 0\ 061$ Gy (6 1 rad)

Femur 13 5 $\phi_{Ba}(F) + 23\ 4\ \phi_{La}(F) = 0\ 166$ Gy (16 6 rad)

Lumbar vertebrae 8 3 $\phi_{Ba}(LV) + 14\ 1\ \phi_{La}(LV) = 0\ 101$ Gy (10 1 rad)

Eyes 12 4 $\phi_{Ba}(E) + 21\ 1\ \phi_{La}(E)$ (see below)

The figures obtained are rough doses calculated on basis of the β-spectra for the systems ^{90}Sr-^{90}Y and ^{140}Ba-^{140}La and the absorption value (45 per cent) may differ in different parts of the skeleton

The ratios $\phi_{Ba}(E)$ and $\phi_{La}(E)$ can be calculated a little more accurately on basis of the choroid concentration of the two nuclides The dose to the inner surface of the choroid (= the dose to the retina) has thus been calculated under the assumptions of a uniform distribution of activity in the approximately spherical shell of the choroid (Fig 3), unit density of the eye (ICRP 23, 1975), and according to the formulas for the β doses from spherical shells as given by LOEVINGER et coll (1956) The γ dose has been considered negligible The β spectra of ^{140}Ba and ^{140}La have been derived from the Radiological Health Handbook

Table

Activity concentration 10[illegible]/injected activity

Time after injection	Sternum			Femur			Lumbar vertebrae			Eyes		
	^{140}Ba/g	^{140}La/g	La/Ba (per cent)	^{140}Ba/g	^{140}La/g	La/Ba (per cent)	^{140}Ba/g	^{140}La/g	La/Ba (per cent)	^{140}Ba/g	^{140}La/g	La/Ba (per cent)
45 minutes				63 1	14 5	23				9 58	1 44	15
3 hours	44 6	19 6	44	76 7	33 7	44	51 9	22 8	44	32 9	11 5	35
24 hours	22 7	22 7	100	56 0	32 2	58	41 1	22 6	55	39 0	20 2	52
6 days	14 4	16 2	112	40 5	40 6	100	26 1	26 1	100	36 8	33 3	91
14 days	9 27	10 7	115	23 8	27 4	115	14 9	17 1	115	25 1	28 9	115
21 days	4 34	4 98	115	13 9	15 9	115	7 77	8 93	115	15 0	17 3	115
28 days	3 72	4 27	115	10 2	11 8	115	5 45	6 27	115	10 2	11 7	115
58 days	0 480	0 554	115	1 52	1 75	115	0 793	0 912	115	1 54	1 77	115
92 days	0 005	0 063	115	0 226	0 260	115	0 096	0 110	115	0 178	0 206	115

Twenty-four hours The soft tissues were at this survival time almost completely cleared from activity but the bone and the ciliary body of the eye still contained activity

Forty-eight hours (Albino mouse in late gestation, Fig 5) Only the skeletal tissues retained the isotope The concentration was lower than that of the maternal skeleton No accumulation was found in the ocular tissues

Six days after the injection on the 13th day of gestation In comparison with the animals injected in late gestation, this mouse had a low uptake of activity in the fetal skeleton A slight uptake was also found in the ciliary body At this survival time like all the others, the spotty uptake of activity observed in certain placental structures was high, indicating that the spots corresponded to calcified loci

Impulse counting technique

Uptake and retention of ^{140}Ba and ^{140}La

The uptake and retention of ^{140}Ba and ^{140}La in the femur, sternum lumbar vertebrae and in the eyes at different times after the injection of the two nuclides in equilibrium are given in the Table

At two weeks after the injection equilibrium between ^{140}Ba and ^{140}La has been achieved in all the organs examined Initially, the concentrations of ^{140}Ba were higher than those of ^{140}La This discrimination was most obvious in the eyes

By regression analysis of the figures from the 14th day after the injection and onwards, the biologic half-lives of Ba in the organs could be determined femur 129 days, sternum 67 days, lumbar vertebrae 73 days and eyes 78 days

Dose calculations

The dose calculations have been based on the retention curves Between day 0 and 14, the surfaces under the curves have been determined planimetrically From the second week after the injection and onwards the retention curves have been approximated by exponential curves that have been received by regression analysis of the retention figures The total dose to a certain organ can be expressed by

$$D(tot) = 0\,512 \left[\int_0^\infty F_{Ba}(t)\ \bar{E}_{Ba}\ \phi_{Ba}(x)\,dt + \int_0^\infty F_{La}(t)\ \bar{E}_{La}\ \phi_{La}(x)\,dt \right] Gy$$

where F(t) are the retention functions (remaining activity per g organ at time t), $\bar{E}$ the mean energies and ϕ the ratio between the true mean dose in the organ 'x' and that in an infinite medium of the same density and in which the concentration of the activities of ^{140}Ba and ^{140}La are the same as those found in the organs The dose contribution from the γ-radiation is negligible as compared to the β-radiation and the mean energies are accordingly equal to the mean β-energies from ^{140}Ba and ^{140}La respectively The numerical values of the mean β-energies ($\bar{E}_{Ba} = 0\,282$ MeV and $\bar{E}_{La} = 0\,490$) have been derived from Radiological Health Handbook (1970)

The ϕ-parameters are unknown The absorbed β-energy from ^{90}Sr-^{90}Y is 32 per cent (PARMLEY et coll 1962) The corresponding figure for ^{140}Ba-^{140}La should be around 45 per cent if the activity distribution can be regarded as equal for the two nuclide systems This might be approximately true for the bone tissue but certainly not for the eyes The micro distribution of the dose in bones is uncertain for ^{90}Sr and ^{90}Y and unknown for ^{140}Ba and ^{140}La

The injection of 37 kBq (1 μCi) ^{140}Ba in equilibrium with ^{140}La would give the following doses

Sternum $4\,9\ \phi_{Ba}(S) + 9\,2\ \phi_{La}(S) = 0\,061$ Gy (6 1 rad)

Femur $13\,5\ \phi_{Ba}(F) + 23\,4\ \phi_{La}(F) = 0\,166$ Gy (16 6 rad)

Lumbar vertebrae $8\,3\ \phi_{Ba}(LV) + 14\,1\ \phi_{La}(LV) = 0\,101$ Gy (10 1 rad)

Eyes $12\,4\ \phi_{Ba}(E) + 21\,1\ \phi_{La}(E)$ (see below)

The figures obtained are rough doses calculated on basis of the β-spectra for the systems ^{90}Sr-^{90}Y and ^{140}Ba-^{140}La and the absorption value (45 per cent) may differ in different parts of the skeleton

The ratios $\phi_{Ba}(E)$ and $\phi_{La}(E)$ can be calculated a little more accurately on basis of the choroid concentration of the two nuclides The dose to the inner surface of the choroid (= the dose to the retina) has thus been calculated under the assumptions of a uniform distribution of activity in the approximately spherical shell of the choroid (Fig 3), unit density of the eye (ICRP 23, 1975), and according to the formulas for the β-doses from spherical shells as given by LOEVINGER et coll (1956) The γ-dose has been considered negligible The β spectra of ^{140}Ba and ^{140}La have been derived from the Radiological Health Handbook

The mean concentrations of the nuclides ^{140}Ba and ^{140}La *in the eyes as given* in the Table, have to be multiplied by 7 5 to correct for the fact that the activity is concentrated in the choroid and not homogeneously distributed over the entire eye

The calculations gave for the outer surface of the retina (i e the inner surface of the choroid)

$$\phi_{Ba}(E) = 1\ 56 \quad \text{and} \quad \phi_{La}(E) = 1\ 24$$

The dose to this region will accordingly be 0 455 Gy (45 5 rad) after an injection of 37 kBq (1 μCi) ^{140}Ba in equilibrium with ^{140}La The dose decreases towards the centre of the vitrious body of the eye The central dose is 27 per cent of that in the retina, i e 0 12 Gy (12 rad)

Discussion

The distribution of ^{133}Ba is similar to that of ^{90}Sr as regards the high uptake in the skeleton Thus there is initially a high concentration in the epiphysial regions and in the periosteum and endosteum, later followed by a predomination of the activity in diaphysial parts of the bones In the membraneous bones of the skull ^{133}Ba (like ^{90}Sr) was taken up strongly initially but was retained to a lesser degree than in the long bones

On the other hand ^{133}Ba seems to have less specific affinity to the hard tissue than ^{90}Sr Four hours after injection of ^{90}Sr activity had practically completely disappeared from the soft tissues with the exception of the excretory pathways However, ^{133}Ba could still, 48 hours after administration, be discerned in the mammary gland In the pancreatic islands, the thyroid and red pulp of the spleen the activity remained at 2 days The most marked soft tissue uptake was in pigmented tissues of the eye and hair follicles In pigmented tissues the activity seemed to be almost as high and long lasting as in the skeleton In albino mice no such uptake was found

^{90}Sr does not accumulate in significant amounts to be detected by autoradiography of the eye Radium on the other hand (TAYLOR et coll) seems to be taken up in dogs in significant amounts in the iris and in combined retinal and choroid samples

Lesions were also observed within 20 days after single and intravenous injection of 370 kBq (10 μCi) of ^{226}Ra per kg body weight These lesions consisted in partial or complete loss of the tapetum and depigmentation of the choroid and iris After relatively low doses, 1 85–12 95 kBq (0 05–0 35 μCi) ^{226}Ra/kg, the lesions were limited to the iris and consisted of hyperpigmented plaques Results of microscopy of the eyes are not yet available, but inspection indicates opacity of the eyes and possible blindness

LAMBERTS & VON ANDEL (1965) have found a fluctuating concentration of ^{133}Ba in the aortic wall of rats The concentration started to rise on the 35th day after the administration of the nuclide, then began to decrease on the 49th day, rose again on the 63rd day, reached a top on the 77th day, fell again and commenced to rise on the 91st day, reaching a maximum level on the 98th day On the 105th day the

concentration was practically 0 The duration of the present autoradiography was unfortunately too short to observe this effect Scintillation counting revealed an activity concentration in the aorta of about 10 per cent of that in the femur 3 hours after the injection The activity in the aorta disappeared, however, rapidly and could not be measured during the period 2 weeks to 3 months after the injection

The calculated radiation doses to the sternum, femur, lumbar vertebrae and pigmented structures of the eye were of a great interest as compared to the carcinogenic ^{90}Sr doses Preliminary results indicate that ^{140}Ba is able to produce tumours of the skeleton (C_{57} Bl mice) at significantly lower dose levels than ^{90}Sr (CBA mice) and that female mice of this strain are much more susceptible to irradiation than males as has been found for ^{90}Sr in the CBA strain (NILSSON 1967) In a group of 50 C_{57} Bl female mice given 55 5 kBq (1 5 μCi) ^{140}Ba per g body weight, 28 per cent had macroscopic bone tumours mainly in the long bones and the spine against 2 per cent in the control group The approximate irradiation dose to the femur in this group was about 5 Gy (500 rad) and 3 Gy (300 rad) to the vertebrae In female CBA mice sarcomas were found in 6 per cent of the mice at a dose level of 1 85 kBq (0 05 μCi) ^{90}Sr/g body weight and in 15 per cent when 3 7 kBq (0 1 μCi) ^{90}Sr/g body weight was given The majority of these tumours were sited in the femur and the doses calculated were 33 and 56 Gy (3 300 and 5 600 rad), respectively One possible explanation for this dose response difference may be wasted irradiation, i e the irradiation exposure to the organ after the formation of the initial malignant clones Such a 'wasted irradiation may even hamper further growth of the cellular proliferation in the clones The initial dose rate from 55 5 kBq (1 5 μCi) ^{140}Ba/g body weight is of course much higher than that after injections of 3 7 kBq (0 1 μCi) ^{90}Sr/g body weight There might also be some strain differences

Acknowledgement

This investigation was carried out as part of the program of European Late Effects Project Group (EULEP)

SUMMARY

The distribution of barium in the mouse has been determined qualitatively by whole body autoradiography after i v administration of ^{133}BaCl$_2$ solution The quantitative distribution of ^{140}Ba and ^{140}La has been analyzed after i p injections of the two nuclides in equilibrium by measuring the activity in excised organs in a two-channel scintillation counter Approximate doses to the eyes and different parts of the skeleton have been calculated

ZUSAMMENFASSUNG

Die Verteilung von Barium in der Maus durch Gesamtkorper Autoradiographie nach intravenoser Administration von ^{133}BaCl$_2$-Losung wurde qualitativ untersucht Die quan

titative Verteilung von ^{140}Ba und ^{140}La wurde nach i p Injektionen dieser beiden Nuclide im Gleichgewicht durch Aktivitätsmessungen der entnommenen Organe in einem Zwei Kanal Scintillationsrechner analysiert Die ungefähren Dosen fur die Augen und die verschiedenen Teile des Skeletts wurden berechnet

RÉSUMÉ

La distribution du baryum dans des souris a été déterminée qualitativement par autoradiographie corporelle totale après administration intra-veineuse d'une solution de $^{133}BaCl$. La distribution quantitative de ^{140}Ba et de ^{140}La a été étudiée après injection intrapéritonéale de ces deux nuclides en équilibre en mesurant l'activité d'organes prélevés au moyen d un compteur à scintillation à deux canaux Les auteurs ont calculé la dose approximative aux yeux et à différentes parties du squelette

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RADIATION THERAPY OF ADRENAL CORTICAL CARCINOMA

B PERCARPIO and A H KNOWLTON

Adrenal cortical carcinoma is a rare malignancy with a reported median survival of less than two years (LIPSETT et coll. 1963) Current accepted management consists of surgical resection of the primary lesion if possible and ortho para DDD chemotherapy for recurrent or metastatic disease Few reports, however, have commented on the clinical response of these tumors to radiation therapy This report presents the experience with 14 patients seen in this hospital

Materials and Methods

The material consisted of 9 males and 5 females with microscopically confirmed adrenal carcinoma, seen since 1952 The age of the patients ranged from 8 to 75 years with a median age of 50 Ten of the primary lesions were left-sided and 4 right-sided Clinical characteristics and result of treatment are given in the Table Five of the patients had sufficiently localized lesions to undergo complete resection Eleven of the 14 developed distant metastases at some time during the course of their disease The remaining 3 patients had residual local tumor or a regional recurrence of the disease The distribution of metastatic disease was similar to that of other reported series (HUTTER & KAYHOE 1966) with lung metastases in 8, liver

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Table

Clinical characteristics and result of treatment

Case No	Age	Metastatic sites	Region irradiated	Gy/days	Response	Survival
1	55	Lung bone and cerebellum	Right supraclavicular fossa	51 00 47	Pain relieved	5 months
2	53	Lung, liver and regional recurrence	Right flank	15 00/7	Pain relieved	12 months
3	42	Lung liver and gastro-intestinal tract	Not irradiated			36 months
4	58	Bone	Lumbar spine	24 00 9	Pain relieved	6 months
5	46	Lung and liver	Not irradiated			3 months
6	69	Regional recurrence	Right flank	28 00 14	Pain relieved	3 months
7	46	Lung, liver and bone	Lumbar spine	38 60/21	Pain relieved	Alive at 29 months
			Right ischium	31 00/15	Pain relieved	
8	10	Regional recurrence	Not irradiated			5 months
9	40	Liver and bone	Preoperative left flank	40 00 28	No regional recurrence	62 months
			Cervical spine	25 00 14	Healed on roentgen examination and pain relieved	
			Lumbar spine	25 00/14	Pain relieved	
			Thoracic spine	21 00 10	Pain relieved	
10	75	None	Preoperative left flank	45 00/40	Tumor regressed on palpation but was unresectable	11 months
11	69	Lung (tumor spilled at surgery)	Postoperative whole abdomen	10 55/10	Local recurrence 34 months after irradiation	59 months
			Postoperative left flank	30 80 26		
12	72	Lung	Postoperative left flank	34 20 36	Local recurrence 8 months after irradiation	17 months
13	45	Liver bone gastro-intestinal tract and para-aortic lymph nodes	Postoperative left flank	28 00 28	No local recurrence	13 5 years
			Right upper quadrant	30 00/22	Pain relieved	
			Pelvis	32 40/22	Rectal obstruction relieved	
			Left lower quadrant	21 00/14	Colonic obstruction relieved	
14	8	Lung	Postoperative left upper quadrant	30 00/28	Local recurrence 2 months after irradiation	3 months

metastases in 6 and bone metastases in 5 patients In addition, intestinal metastases developed in 2 cases and metastases of the central nervous system appeared in one Clinically evident functioning tumors occurred in 8 of the 14 cases with laboratory evidence for endocrine abnormalities documented in all 8 Virilization or percocious puberty appeared in 4 patients, feminization in 2 patients and 2 displayed Cushing s syndrome

A total of 18 courses of external irradiation were administered to 11 of these patients The remaining 3 patients were not irradiated on account of a grave immediate prognosis or a diffuse disease that could not be localized with sufficient exactitude for palliative treatment Irradiation was given 5 days per week and no patient received chemotherapy at the same time as irradiation Tumor doses ranged from 15 to 51 Gy (1 500 to 5 100 rad) in 7 to 47 days Twelve of the treatment courses were palliative and evaluable for response by either palpable tumor size, reduction in pain, relief of localized intestinal obstruction or radiographic changes All 12 were considered to have had adequate palliation by irradiation (Table) Functioning and non-functioning tumors responded equally well and neither sex nor age seemed to affect the response to radiation None required subsequent local retreatment except for Case 7 who required decompressive lumbar laminectomy for recurrent tumor 15 months following 38 6 Gy (3 860 rad) of palliative lumbar spine irradiation

Preoperative irradiation was attempted in 2 patients but successful local resection without subsequent local recurrence was possible in only one (Case 9) In the other patient (Case 10) the tumor decreased in size following 45 Gy (4 500 rad) but was considered unresectable on the basis of radiographic findings

Four patients (Cases 11, 12, 13 and 14) received postoperative flank irradiation for unresectable lesions or possible tumor spillage at the surgery Recurrence appeared in 3 of these patients at 2, 8 and 34 months following treatment A notable exception was Case 13, who had no local recurrence for 11 years until other abdominal disease of similar microscopy became evident

The median survival of all patients from the time of diagnosis was 12 months with only 2 surviving longer than 5 years Chemotherapy, usually with ortho para DDD, was given to 9 of these patients with varying results

Discussion

The role of radiation in the management of adrenal cortical carcinoma has been described infrequently and with little documentation in the literature POHLE (1950) considered these tumors not to be responsive to irradiation, whereas PORTMANN (1950) obtained satisfactory palliation occasionally but offered no documentation of this WALTON et coll (1955) found little evidence of the response of these malignancies to irradiation but classified them as moderately sensitive MACFARLANE (1958) did not consider radiation to be of great value Of the 38 patients reported by LIPSETT et coll, 18 underwent definitive surgery and 5 of these received local irradia-

tion of at least 30 Gy (3 000 rad) They did not comment on local control of in this subgroup, but termed these neoplasms radiation resistant and did not mend irradiation in their management A large series of 138 patients was re by HUTTER & KAYHOE who recommended chemotherapy with ortho para DD inoperable functioning and non functioning adrenal carcinomas He stated radiation therapy had not been shown to be effective in the treatment of inope lesions, but gave no data concerning this from his group of patients MURPHY (1 irradiated 6 patients with adrenal tumors without any appreciable alteration in th course of the disease, but felt that the treatment served a palliative function The Memorial Hospital chemotherapy experience with 34 patients was reviewed by HUVOS et coll (1970) Seventeen of these patients received irradiation as some part of their management but dosage and response were not stated HARRISON et coll (1973) made no clear recommendations for the role of radiation therapy in their review of 18 patients The most enthusiastic proponents of postoperative irradiation for operable adrenal cortical carcinomas in children have been STEWART et coll (1974) They administered whole abdominal irradiation to 4 children with this tumor without chemotherapy and had 3 survivors without recurrence at 1 to 6 years of follow up One of these survivors had an unresectable tumor invading the vena cava initially but was free of tumor on re exploration following radiation therapy They recommended a minimum dose of 25 Gy (2 500 rad) of abdominal irradiation with shielding of the contralateral kidney and adrenal gland The M D Anderson Hospital experience with 32 patients was reviewed by HAJJAR et coll (1975) who concluded that radiation therapy had no demonstrable effect on the primary tumor or its metastases The more popular current textbooks of radiation therapy make no comment on irradiation of this tumor (BUSCHKE & PARKER 1972, FLETCHER 1973, MOSS et coll 1973) Although human adrenal cortical carcinoma has been cultured in vitro (LEIBOVITZ et coll 1973), there has been no reported biologic investigation of its relative sensitivity to irradiation

In contrast to most reports in the literature, the present series of patients indicates that metastases of adrenal cortical carcinoma are responsive to palliative doses of irradiation The pain of metastases is relieved, osseous lesions may show radiographic evidence of healing and localized intestinal obstruction can be alleviated Doses of approximately 30 to 40 Gy (3 000 to 4 000 rad) delivered in 2 to 3 weeks are to be recommended for adequate palliation On occasion, prolonged local control of unresectable lesions may be obtained with similar doses

SUMMARY

The role of radiation therapy in the management of adrenal cortical carcinoma has had little documentation in the literature Fourteen patients with this malignancy were given 18 courses of palliative, preoperative or postoperative irradiation The clinical results are presented Significant palliation was obtained in all patients along with occasional long term local control of unresectable lesions.

ZUSAMMENFASSUNG

Die Rolle der Strahlentherapie bei der Behandlung des Karzinoms der *Nebennierenrinde* ist in der Literatur nur wenig diskutiert Vierzehn Patienten mit dieser malignen Erkrankung wurden palliativ, präoperativ oder postoperativ bestrahlt Die klinischen Ergebnisse werden vorgelegt Bei allen Patienten wurde eine signifikante Palliation mit *gelegentlich langan*-haltender lokaler Kontrolle der nichtresezierbaren Veränderungen erreicht

RÉSUMÉ

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FROM THE INSTITUTE OF PATHOLOGY, THE E N T DEPARTMENT, AND THE RADIUM CENTRE, MUNICIPAL HOSPITAL, UNIVERSITY OF ÅRHUS, DK 8000 ÅRHUS, DENMARK

EPIDERMOID CARCINOMA OF THE LARYNX

VI Histologic grading in the clinical evaluation

C LUND, H SØGAARD K JORGENSEN and M HJELM HANSEN

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Microscopic grading of the malignancy of laryngeal epidermoid carcinomas as a prognostic adjuvant to clinical evaluation has been discussed by MUSTAKALLIO (1946) MCGAVRAN (1961) and JACOBSSON (1973) The grading system introduced by JACOBSSON (glottic carcinoma) was slightly modified and used on a series of carcinoma of the lip (LUND et coll 1975 a) and of carcinoma of the tongue (LUND et coll 1975 b) It was found to give essential data supplementary to the clinical evaluation A similar analysis of a series of laryngeal carcinoma is now presented and in addition some aspects on the biologic effect of irradiation are included

Material The original series comprised 152 patients with carcinoma of the larynx treated during the period 1963 to 1968 Analyses of the clinical and biologic effect of irradiation in this series have previously been published (JORGENSEN & SELL 1971, JORGENSEN 1974, HJELM HANSEN et coll 1975) In 23 cases microscopic material

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Table 1

Laryngeal carcinoma Microscopy of 129 biopsies

Region	Appearance	Cytoplasmic differentiation	Nuclear differentiation	Mitosis	Mode	Depth	Vascular invasion	Cellular response	Average microscopic score
Glottis (90 cases)									2 46
No of estimated parameters	86	90	90	90	83	25	86	86	
No of points	226	190	285	217	208	57	154	219	
Parameter score	2 6	2 1	3 2	2.4	2.5	2.3	1 8	2.5	
Supraglottis (33 cases)									2 80
No of estimated parameters	32	33	33	33	31	4	31	31	
No of points	92	86	111	92	89	10	77	90	
Parameter score	2 9	2.6	3 4	2.8	2 9	2.5	2 5	2 9	
Subglottis (6 cases)									2.85
No of estimated parameters	6	6	6	6	6	1	5	4	
No of points	17	15	22	16	16	1	13	12	
Parameter score	2 8	2 5	3 7	2 7	2 7	1 0	2 6	3 0	
Total (129 cases)									2 57
No of estimated parameters	124	129	129	129	120	30	122	121	
No of points	335	291	418	325	313	68	244	321	
Parameter score	2 7	2 3	3 2	2.5	2 6	2 3	2 0	2 7	

from laryngeal carcinoma One died of haemorrhage from an ulcerated vessel in the larynx the other of distant metastases

Microscopy Carcinoma of the larynx is almost exclusively of the epidermoid type, but of a varying degree of differentiation and variable mode of growth This affords a multifactorial microscopic grading comprising both the tumour-cell population and the tumour host relationship

The grading system includes 8 parameters each graded from 1 to 4 Each parameter and grade was defined so accurately that comparable and reproducible results were obtained (see Table 3, LUND *et coll 1975 b*, p *515)* The microscopy was performed without knowledge of the clinical analysis For each specimen a maximum score of 32 (8 × 4) was possible, but all 8 parameters could not be assessed in every specimen Accordingly, a *score*, defined as the sum of points divided by the number of parameters assessed was used

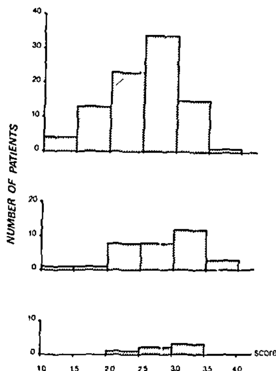


Fig 1 Distribution of the total series of 129 cases of laryngeal carcinoma in relation to microscopic score (The white line indicates the average score) Top = glottic carcinoma, 90 cases Middle = supraglottic carcinoma, 33 cases Bottom = subglottic carcinoma, 6 cases

from the primary biopsy was not available The following analyses are based upon biopsies from the primary tumours in the remaining 129 patients No other selection has been made, and no differences in clinical condition or course from the original series have occurred

Clinical aspects Primarily 126 of the 129 patients were treated with ^{60}Co radiation and 3 were operated upon

Local recurrence developed or residual tumour occurred in 40 per cent of the entire series (52/129), in 36 per cent (32/90) of the glottic group, in 48 per cent (16/33) of the supraglottic, and in 67 per cent (4/6) of the subglottic group

Regional lymph-node metastases occurred in 21 per cent (27/129) of the entire series, in 12 per cent (11/90) of the glottic group, in 45 per cent (15/33) of the supraglottic and in 17 per cent (1/6) of the subglottic group

The carcinoma death rate was 23 per cent (30/129) in the entire series, 13 per cent (12/90) in the glottic, 48 per cent (16/33) in the supraglottic, and 33 per cent (2/6) in the subglottic group

In the group of patients with regional lymph-node metastases the death rate was 59 per cent (16/27) and in the group with local recurrence or residual tumour 48 per cent (25/52)

In the group with local recurrence or residual tumour without lymph-node metastases the death rate was 32 per cent (12/37) Two patients without local recurrence or residual tumour, nor regional lymph-node metastases were classified as deaths

Table 2 (*cont*)

Mitosis	Mode	Depth	Vascular invasion	Cellular response	Average microscopic score
90/217 2 4	83/208 2.5	25/37 2 3	86/154 1 8	86/219 2.5	2 46
58/136 2.3	55/132 2 4	16/38 2 4	56/ 98 1 7	55/141 2 6	2 43
32/ 81 2 5	28/ 75 2 7	9/19 2 1	30/ 56 1 9	31/ 77 2 5	2 51
79/189.2 4	73/179 2 5	22/49 2 2	78/138 1 8	76/192 2.5	2 43
11/ 28 2.5	10/ 28 2 8	3/ 8 2 7	8/ 16 2 0	11/ 28 2.5	2.69
78/186 2 4	72/174 2 4	23/51 2 2	76/132 1 7	74/190 2.6	2.41
12/ 31 2 6	11/ 34 3 1	2/ 6 3 0	10/ 22 2 2	12/ 29 2 4	2 80
33/ 92 2 8	31/ 89 2 9	4/10 2 5	31/ 77 2 5	31/ 90 2 9	2 80
17/ 49 2.9	16/ 46 2.9	1/ 2 2 0	16/ 35 2 2	16/ 46 2.9	2 77
16/ 43 2 7	15/ 43 2 9	3/ 8.2.7	15/ 41 2 7	15/ 44 2.9	2.83
18/ 49 2 7	16/ 42 2 6	3/ 9 3 0	16/ 35 2 2	16/ 42 2 6	2 64
15/ 43 2 9	15/ 48 3 2	1/ 1 1.0	15/ 40 2.7	15/ 48 3 2	3 01
17/ 52 3 1	17/ 44 2 6	2/ 5 2 5	16/ 37 2 3	16/ 44 2.7	2 73
16/ 46 2 9	15/ 44 2 9	3/ 6 2 0	15/ 39 2.6	15/ 46 3 1	2 87
6/ 16 2 7	6/ 16 2 7	1/ 1 1 0	5/ 13 2 6	4/ 12 3 0	2.85
2/ 4 2 0	2/ 5 2 5	0/ 0 0 0	2/ 5 2 5	2/ 7 3 5	2 57
4/ 12 3 0	4/ 11 2 7	1/ 1 1 0	3/ 8 2 7	2/ 5 2 5	3 00
5/ 13 2.6	4/ 10 2 5	1/ 1 1 0	4/ 10 2 5	4/ 13 3 2	2 82
1/ 3 3 0	1/ 3 3 0	0/ 0 0 0	1/ 3 3 0	1/ 2 2 0	3 00
4/ 11 2 7	4/ 13 3 2	0/ 0 0 0	4/ 12 3 0	3/ 9 3 0	2 87
2/ 5 2 5	2/ 5 2 5	1/ 1 1 0	1/ 1 1 0	1/ 9 9 0	2 83
129/325 2 5	120 313 2 6	30 68 2 3	122/244 2.0	121/321 2 7	2 57

case of verrucous carcinoma which is stated to make up 1 to 2 per cent of laryngeal carcinomas (VAN NOSTRAND et coll 1972)

Clinical and microscopic correlation The microscopic score was compared with the frequency of (1) local recurrence or residual tumour, (2) regional lymph-node metastases, (3) fatal cases, and (4) T-classification

Table 2 gives the comparison between clinical assessment and microscopic grading as well as the relative influence of the individual parameters upon the microscopic

Table 2

Laryngeal carcinoma Relationship between clinical state and microscopic grading
(Parameters estimated/No points parameter score)

Region	No of cases	Appearance	Cytoplasmic differentiation	Nuclear differentiation
Glottis				
Total	90	86/226 2 6	90/190 2 1	90/285 3 2
No recurrence	58	56/148 2 6	58/123 2 1	58/181 3 1
Recurrence	32	29/ 77 2 7	32/ 71 2 2	32/104 3 2
No metastases	79	75/196 2 6	79/165 2 1	79/249 3 2
Metastases	11	10/ 29 2 9	11/ 28 2 5	11/ 36 3 3
Not dead from carcinoma	78	74/193 2 6	78/259 3 3	78/241 3 1
Dead from carcinoma	12	12/ 33 2 7	12/ 31 2 6	12/ 44 3 7
Supraglottis				
Total	33	32/ 92 2 9	33/ 86 2 6	33/111 3 4
No recurrence	17	17/ 48 2 8	17/ 37 2 2	17/ 58 3 4
Recurrence	16	15/ 44 2 9	16/ 49 3 1	16/ 53 3 3
No metastases	18	17/ 47 2 8	18/ 35 1 9	18/ 58 3 2
Metastases	15	15/ 45 3 0	15/ 40 2 7	15/ 53 3 5
Not dead from carcinoma	17	17/ 48 2 8	17/ 34 2 0	17/ 55 3 2
Dead from carcinoma	16	15/ 44 2 9	16/ 42 2 6	16/ 56 3 5
Subglottis				
Total	6	6/ 17 2 8	6/ 15 2 5	6/ 22 3 7
No recurrence	2	2/ 5 2 5	2/ 3 1 5	2/ 7 3 5
Recurrence	4	4/ 12 3 0	4/ 14 3 5	4/ 15 3 7
No metastases	5	5/ 14 2 8	5/ 16 3 2	5/ 18 3 6
Metastases	1	1/ 3 3 0	1/ 3 3 0	1/ 4 4 0
Not dead from carcinoma	4	4/ 11 2 7	4/ 10 2 5	4/ 15 3 7
Dead from carcinoma	2	2/ 6 3 0	2/ 7 3 5	2/ 7 3 5
Larynx				
Total	129	124/335 2 7	129/291 2 3	129/418 3 2

Fig 1 illustrates the distribution of the microscopic scores for glottic, supraglottic, and subglottic carcinomas, divided into 6 score intervals In the following analyses only 2 intervals were employed, arbitrarily separated at 2 50 These two subgroups are uniform with regard to sex, age, and treatment Growth in depth could be assessed in only 23 per cent (30/129) of all biopsies (Table 1) This may influence the evaluation of the other parameters, which often have a higher score in the depth of an infiltrating lesion

One case of small-cell anaplastic carcinoma was included in the series, but no

Table 2 (*cont*)

Mitosis	Mode	Depth	Vascular invasion	Cellular response	Average microscopic score
90 217 2 4	83/208 2 5	25/57 2.3	86/154 1 8	86/219 2.5	2.46
58 136 2 3	55/132 2.4	16/38 2.4	56/ 98 1 7	55/141 2 6	2.43
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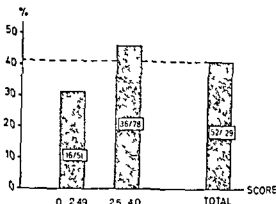


Fig 2 Laryngeal carcinoma, 129 cases Frequency of local recurrence or residual tumour in relation to microscopic score

score It is apparent that on microscopic evaluation the supraglottic and subglottic carcinomas are of a more malignant nature than those in the glottic region, and also that practically all 8 parameters exert an influence upon this difference

Local recurrence and residual tumour The frequency of local recurrence or residual tumour was somewhat higher at a microscopic score exceeding 2 5 (Fig 2), 46 per cent (36/78) at the higher and 31 per cent (16/51) at the lower score level, although the difference is not statistically significant

The influence of radiation therapy upon the frequency of local recurrence was estimated by calculating the biologic effect in each individual case as recommended by ELLIS (1968, 1969) and by WINSTON et coll (1969) The biologic effect of each individual irradiation is stated in terms of PT_{1800} in ret (partial tolerance of normal connective tissue when NSD = 1 800 ret) The values are presented in Fig 3

The glottic series was arbitrarily divided into two sub-groups, one with a high and one with a low score, the limit being at ~2 5 These sub-groups were related to 3 ranges of biologic effect of irradiation less than 1 600 ret, 1 600-1 700 ret, and more than 1 700 ret The result appears in Fig 4, which reveals a falling frequency of local recurrence at increasing ret levels It is also evident that the sub-group with a high score had a higher local recurrence rate at all ret levels

Regional lymph-node metastases Within the entire series the frequency of regional lymph node metastases in relation to the microscopic score (Fig 5) was significantly higher at a score exceeding 2 5 ($0.025 < p < 0.05$) When the series is divided into the 3 regions, the difference in the glottic group proved to be small (4 per cent, Table 3), whereas in the supraglottic group it was marked (37 per cent, Fig 6), close to the 5 per cent significance limit, even in this small group

Death rate The frequency of deaths from carcinoma in relation to the microscopic score increases for the entire series (Fig 7) at a higher score with a statistically significant difference at a score below and over 2 5, respectively, viz 12 per cent (6/51) versus 31 per cent (24/78, $0.01 < p < 0.025$)

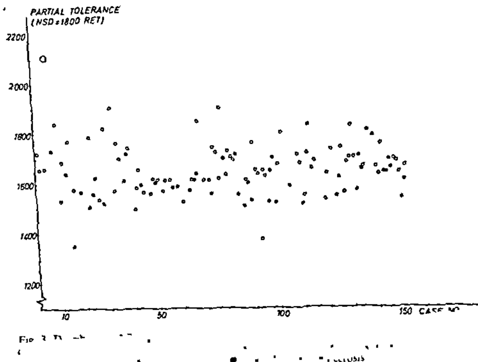


Fig. 3 ... necrosis

Table 3

Glottic carcinoma (90 cases) Relationship between the frequency of regional lymph node metastases and microscopic score in the T1 to T4 groups

	Microscopic score		Total	Per cent
	0–2 49	2 50–4 0		
T1 group				
Number	2/25	1/23	3/48	6
T2 group				
Number	0 8	2/12	2/20	10
T3 group				
Number	1/6	2/12	3/18	17
T4 group				
Number	1/1	2/3	3/4	75
Total				
Number	4/40 (10%)	7/50 (14%)	11/90	12

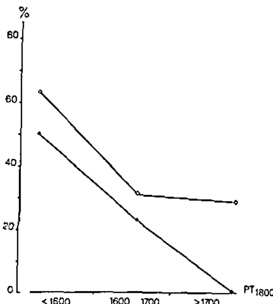


Fig 4 Glottic carcinoma 85 cases Frequency of local recurrence or residual tumour in relation to PT_{1800} in the glottic carcinomas with low and high microscopic score Microscopic score ◇ ≥ 2 5, ◆ < 2 5

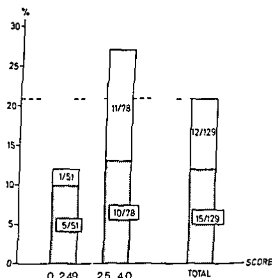


Fig 5 Laryngeal carcinoma 129 cases Frequency of regional lymph node metastases in relation to microscopic score in the total laryngeal series ▭ 12 primary ▭ 15 secondary metastases

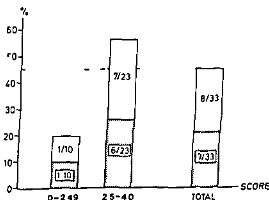


Fig 6 Supraglottic carcinoma 33 cases Frequency of regional lymph node metastases in relation to microscopic score in the supraglottic series ▭ = 8 primary ▭ = 7 secondary metastases

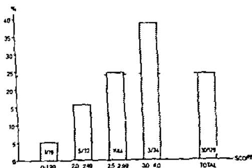


Fig 7 Laryngeal carcinoma 129 cases Frequency of deaths from carcinoma in relation to microscopic score in the total laryngeal series

T-classification Relating the frequency of regional lymph node metastases to the microscopic score within the individual T-group (Tables 3, 4) revealed an increasing tendency with increasing T-grouping A definite tendency also existed to an increased metastatic rate at the higher score level within the individual T-group This was most evident in the supraglottic series

Discussion

The importance of microscopic grading of malignant tumours was first pointed out by BRODERS (1920, 1926, 1940) on epidermoid carcinomas Originally, BRODERS used a monofactorial system based upon the relative degree of cellular differentiation, but later he emphasized the importance of growth into the depth

The importance of microscopic grading of laryngeal carcinomas was emphasized

Table 4

Supraglottic carcinoma (33 cases) Relationship between the frequency of regional lymph node metastases and microscopic score in the T1 to T4 groups

	Microscopic score		Total	Per cent
	0-2 49	2 50-4 0		
T1 group				
Number	1/4	1/6	2/10	20
T2 group				
Number	0 2	5/6	5/8	63
T3 group				
Number	0 0	4/5	4/5	80
T4 group				
Number	1/4	3 6	4/10	40
Total				
Number	2/10 (20 %)	13/23 (57 %)	15/33	46

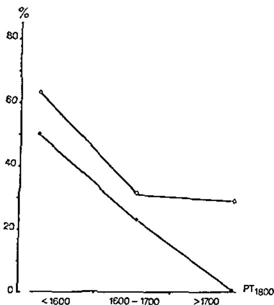


Fig 4 Glottic carcinoma, 85 cases Frequency of local recurrence or residual tumour in relation to PT_{1800} in the glottic carcinomas with low and high microscopic score Microscopic score ◇ ≥ 2 5, ◆ < 2 5.

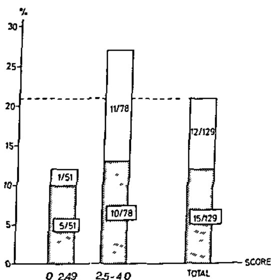


Fig 5 Laryngeal carcinoma, 129 cases Frequency of regional lymph node metastases in relation to microscopic score in the total laryngeal series ▭ – 12 primary, ▭ – 15 secondary metastases

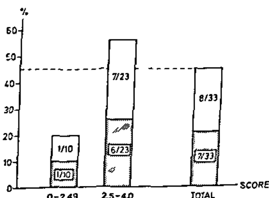


Fig. 6 Supraglottic carcinoma, 33 cases Frequency of regional lymph node metastases in relation to microscopic score in the supraglottic series ▭ – 8 primary, ▭ – 7 secondary metastases

microscopic score at 3 ranges of partial tolerance (Fig 4) The number of patients is small and the differences observed are not statistically significant, but a clear tendency exists a low score is accompanied by a low local recurrence rate at the same ret level If the same tendency may be encountered in a larger material, this may involve therapeutic consequences In the present assessment of the parameters (Table 2) the sum of the individual parameters seems to be decisive A more thorough analysis is possible when the primary biopsy specimens are fully representative, allowing all parameters to be appraised By a more representative biopsy as well as by improved preparation the microscopic grading system may be rendered still more reliable and possibly further extended

On the basis of the accumulated experiences, microscopic grading of all epidermoid carcinomas within the head-neck area has been performed since September 1974 At present, the grading system is considered a valuable supplement to the clinical evaluation Patients with tumours of a high microscopic score are controlled at shorter intervals than others The material is still too small to suggest therapeutic consequences for the treatment of primary tumours with a high microscopic score, but it is conceivable that modification of the radiation therapy, exploratory operations and possibly elective neck dissections will come into use

Conclusion

A statistically significant correlation between microscopic score (degree of malignancy) and the frequency of regional lymph-node metastases and death rate was revealed Tumours with a high microscopic score had a distinctly higher frequency of local recurrence at all ret levels Moreover, the increased metastatic rate at a higher score was found not only with increasing T stage, but also within the individual T groups Thus the microscopic grading has proved to afford important supplementary information in laryngeal carcinoma, which is of particular importance at the lower T stages As a first consequence of the grading system used, a closer follow up of patients with a tumour of a high microscopic score is introduced

SUMMARY

A multifactorial microscopic grading of malignancy was performed [illegible]
examined series [illegible]
tically significa[illegible]
the death rate [illegible]
[illegible] information for the T-classification and for the prognosis Microscopic grading is an essential supplement to the clinical evaluation of risk groups

ZUSAMMENFASSUNG

Eine multifaktorielle mikroskopische Gradierung der Malignität wurde aufgestellt und in einer klinisch gut untersuchten Serie von 129 Patienten mit einem Larynxkarzinom benutzt Der mikroskopische Gradierungswert war statistisch signifikant zur Frequenz der

by MUSTAKALLIO In a series of 67 laryngeal carcinomas he found that primary surgery was not advisable of undifferentiated tumours (BRODERS' grade IV) In his opinion, the result of microscopic grading ought to have therapeutic consequences In a major series MCGAVRAN et coll observed a definite correlation between the differentiation of the tumour cells and the frequency of regional lymph-node metastases PAAVOLAINEN (1970) investigated the reaction of the stroma in laryngeal carcinomas and found that an increased occurrence of acid mucopolysaccharides caused a statistically significant increase in the frequency of local recurrence and corresponding impairment of the prognosis BENNETT et coll (1971) in a series of 24 patients, investigated the role of the suggestive immune reactivity of the host organism, expressed in the degree of local lymphocytic response and reactivity in the regional lymph nodes The result suggested that local lymphoid infiltration was a favourable prognostic sign in highly differentiated epidermoid carcinomas

The two fundamental factors in the system of BRODERS, the tumour cell population and the tumour-host relationship, were extended by JAKOBSSON to comprise 4 parameters each Applying this multifactorial grading system to 230 cases of glottic carcinoma, he found a distinct correlation between the result of microscopic grading and recurrence rate as well as prognosis At the same time, he analysed the parameters, which may be said to be an amendment of the system

This multifactorial grading system was modified for practical reasons by an exact definition of each parameter and grade, and for calculation purposes by introducing a score (LUND et coll 1975 a) A statistically significant correlation between the microscopic score and the frequency of local recurrence as well as of regional lymph-node metastases and the death rate was found in a series of 438 patients with carcinoma of the lip In a series of 49 carcinomas of the tongue a statistically significant correlation between the score and the frequency of regional lymph-node metastases was observed, but only a tentative correlation to the frequency of local recurrence (LUND et coll 1975 b) In both series important supplementary data for the T-classification were recorded A distinctly higher metastatic rate at a higher microscopic score within the individual T-groups existed

The present analysis of the microscopic grading of 129 cases of laryngeal carcinoma disclosed a statistically significant correlation between the microscopic score and the frequency of regional lymph-node metastases A definite correlation between the metastatic rate and the score was also found in the individual T-groups, most evident in the supraglottic series The same distinct correlation was found between microscopic score and death rate

An analysis of the correlation between the score and the frequency of local recurrence or residual tumour disclosed only a relatively slight tendency to an increased local recurrence rate at higher score level This is, in fact, in accordance with the clinical findings, viz the recurrence rate is not as important a prognostic factor as the frequency of regional lymph node metastases An analysis of particular problems concerning local recurrences after radiation therapy were made at a high and a low

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RADIATION THERAPY OF NASOPHARYNGEAL CARCINOMA IN EAST AFRICA

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Nasopharyngeal carcinoma has a unique geographic distribution. In some parts of the world it is extremely frequent as in southern China, Hong Kong, Formosa and Singapore (10–15 cases/100 000 and year), while its incidence in other parts of the world such as Europe, North America, South Africa, India and Japan is low (0–1 cases/100 000 and year). An intermediate incidence is encountered in some areas of East and North Africa, and Kenya belongs to this region (1–10 cases/100 000 and year). The incidence in Kenya is, probably, about 5 times higher than in Europe (CLIFFORD 1970). Apart from its remarkable geographic distribution, the relation to Epstein Barr virus has greatly increased the interest for this tumour. Due to the collaboration between the Institute of Tumor Biology in Stockholm and the ENT-department at the Kenyatta National Hospital in Nairobi, concerning the association between Burkitt's lymphoma and nasopharyngeal carcinoma with the Epstein–Barr virus (see KLEIN 1973, for a review), it was decided that a radiation thera-

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regionalen Lymphknotenmetastasen und zur Mortalitätsrate korreliert und bietet bedeutende zusätzliche Information zur T-Klassifikation und zur Prognose Die mikroskopische *Gradierung ist ein wesentliches Supplement zur klinischen Erfassung von Risikogruppen*

RÉSUMÉ

Les auteurs ont établi une gradation multifactorielle microscopique de la malignité sur une série de 129 malades atteints de cancer du larynx bien examinés cliniquement Les nombres de points microscopiques présentent une forte corrélation statistique avec la fréquence des métastases lymphatiques régionales et avec le taux de mortalité Ils ont apporté *une information supplémentaire* importante pour la classification T et pour le pronostic Cette gradation microscopique est un complément essentiel de l evaluation clinique des groupes de risque

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Table 2

Duration of symptoms before admission

Duration (months)	No of cases
0–3	6
3–6	9
6–12	20
12–24	16
>24	8
No information	5
Total	64

Duration of history before admission Most patients had a long history with symptoms from the primary tumour or cervical node metastases before admission to hospital (Table 2) The majority reported a history of more than 6 months and, in about one third of the cases, the history covered more than one year Although European series may number many cases with a surprisingly long history before admission (GODTFREDSEN 1944), this was more marked in the present African series, which is in good agreement with the advanced stage of most tumours

Microscopy was not re evaluated The classification made by the pathologist at the primary diagnosis was used The majority of the tumours were described as anaplastic or poorly differentiated carcinoma (54 cases) In only 5 cases in this series, the lesion was more differentiated and classified, in 2 cases as squamous cell carcinoma in 2 cases as cylindric cell carcinoma and in one as a malignant pleomorphic adenoma Reticulum cell sarcoma was diagnosed only once, but in a further 4 cases with anaplastic tumours, the pathologist was unable to decide between anaplastic carcinoma and reticulum cell sarcoma It is well known that in areas with high incidence of nasopharyngeal carcinoma the proportion of anaplastic or poorly differentiated carcinomas is even larger than in low incidence areas (YEH 1962)

Extension of the disease Despite the previously mentioned selection, most patients had very advanced disease The primary tumour was often huge, could be palpated from the mouth and often extended outside the nasopharynx (Table 3) Neck node involvement was found in 53 patients (82 per cent) Most striking was the size of these nodes, which often formed huge bulging masses involving also the lower part of the neck (Table 4, where 'large' denotes a continuous mass, 5 cm × 5 cm or larger, and 'small' nodes of 1 cm or less)

Most patients were, despite advanced disease and prolonged history, in remarkably good general condition

Table 1

Sex and age Average age 38 years

Age (years)	Males	Females	No of cases
0–9	1	0	1
10–19	3	3	6
20–29	7	2	9
30–39	8	6	14
40–49	13	7	20
50–59	8	2	10
60–69	3	1	4
70–	0	0	0
Total	43	21	64

Material

Patient selection Carcinoma of the nasopharynx in East Africa is, at the time of admission to the hospital, often very advanced with huge cervical lymph node metastases and extensive destruction of the base of the skull, resulting in serious cranial nerve symptoms (CLIFFORD et coll 1968) Due to the limited resources of the department, it was, from the start, decided that patients with radiologically detectable lesions of the base of the skull, would not be admitted for irradiation This selection was, however, not rigorously followed and a small number of cases with erosion of the base of the skull were, in fact, included in this series No limits were used for admission of patients as regards the size and extension of the nodal disease in the neck

Up to the end of 1970, that is, during the first 2 years of activity, a total of 64 cases were admitted for radiation therapy This series was analyzed by one of the present authors (L -G L) during a stay in Nairobi from October 1971 to April 1972 By then, the observation time for all patients ranged from one to three years

Race, sex and age All patients in this series were Africans Sex and age are summarized in Table 1 The male/female ratio was about 2 1 and thus similar to that reported from most European, Asian and American series The patients were remarkably young with a mean age of only 38 years, which is quite different from what is found in European series, for which the mean age of the patients usually is 50 to 60 years (Ho 1972) In spite of great differences in age distribution in the general population in Kenya and in Europe, it seems likely that there is a true difference in age distribution of NPC between high and low incidence areas Such a difference was found, for example, between Sweden and Hong Kong, when age-specific incidences were compared (Ho)

Table 5

Anatomic point indices

Extension of the tumour disease	Points
System I	
No lymph node metast	1
Unilat lymph node metast	2
Bilat. lymph node metast	3
System II	
Primary tumour	
Confined to nasoph	1
Extension outside nasoph	2
Erosion of base of skull	3
Cervical lymph nodes	
Unilat metast	1
Bilat metast	2
Large metast (≥ 5 cm × 5 cm)	1
Involving lower half of neck	1

roentgenologically In total, 19 patients presented with erosion of the skull base with or without cranial nerve symptoms

Treatment Irradiation was given with a ^{60}Co-kilocurie unit As a rule, the primary tumour and both sides of the neck were irradiated whether lymph node metastases were found or not The primary site of the tumour received in most cases a tumour dose of 5 500 to 6 700 rad in 30 to 55 days and the cervical region a tumour dose of 4 500 to 6 500 rad during the same time Both the primary tumour and the neck were irradiated daily during 5 days per week. The primary site was irradiated from two lateral opposing fields, sometimes supplemented by one anterior field The neck region was usually irradiated from two large opposing fields, one anterior and one posterior, with a narrow lead shield in the midline for protection of spinal cord, larynx and trachea Careful individual isodose planning was performed During the second half of the period, starting from October 21, 1969, 'prophylactic' treatment was given also to the mediastinum and both axillae in most patients These regions usually received about 4 000 rad in 30 days

In 4 patients only the primary tumour was treated, in 32 patients the primary tumour and both sides of the neck, while the remaining 28 received treatment to the primary tumour, the neck, both axillae and the mediastinum Most patients tolerated the treatment well with skin reaction limited to a moderate dry epidermitis and in some cases small patches of moist epidermitis on the lateral parts of the neck One patient died during treatment Three refused further treatment after having received 1 000, 1 800 and 4 300 rad, respectively, to the primary tumour In 2, treatment was discontinued due to the appearance of generalized metastases and, in another 2, general

Table 3

Extension of the disease

Primary tumour	Lymph node metastases			No of cases
	None	Unilat	Bilat	
Confined to nasopharynx	3	12	17	32
Extending outside nasopharynx but base of skull not eroded	5	8	6	19
Base of skull eroded	3	3	7	13
Total	11	23	30	64

Table 4

Size and site of cervical metastases

Site	Size			No of cases
	Large	Moderate	Small	
Confined to upper half of neck	14	4	3	21
Involving also lower half of neck or supraclavicular fossa	26	5	1	32
Total	40	9	4	53

Methods

Pretreatment examination All cases were submitted to routine physical examination, supplemented by direct and indirect nasoscopy Biopsies were taken from the nasopharynx and, if palpable nodes were present, from one side of the neck Cranial nerve function was tested at the E N T department Chest and skull films were obtained routinely before treatment Facilities for tomography were not available

Clinical staging In order to compare different populations in this series, two staging systems were used (Table 5) In system I, only the occurrence of neck node metastases was taken into account For numerical prognostic analysis a case was given 1, 2 or 3 points if there were no, unilateral or bilateral metastases, respectively System II was a more complicated point system, which, apart from the size and extension of the neck node metastases, also took into account the extension of the primary tumour As seen in Table 5, the number of points could vary from 1 (primary tumour limited to nasopharynx without cervical involvement) up to 7 (erosion of base of the skull and bilateral large metastases, involving also lower half of the neck) In the group 'erosion of the skull base', also cases with cranial nerve symptoms or signs were included, which were recorded in 8 patients Of these, 2 had basal erosion

Table 7

Results after treatment related to the anatomic point indices

	One year			Two years		
	No of cases	Point index system		No of cases	Point index system	
		I	II		I	II
Cured	20 (31 %)	1.7	3.0	6 (16 %)	1.7	2.0
Failures	31	2.6	5.1	22	2.5	4.5
No information	13	2.5	4.5	10	2.5	4.8

Table 8

Results after treatment related to the presence of lymph node metastases

	One year			Two years		
	Lymph node metastases			Lymph node metastases		
	None	Unilat	Bilat	None	Unilat	Bilat
Total number of patients	11	23	30	5	14	19
Cured	9	7	4	3	2	1
Failures	2	9	20	2	7	13
No information	0	7	6	0	5	5
Minimum cure rate (per cent)	82	30	13	60	14	5

Table 9

Results after treatment related to the anatomic point indices

	One year							Two years						
	Anatomic index points							Anatomic index points						
	1	2	3	4	5	6	7	1	2	3	4	5	6	7
Total number of cases	3	6	8	14	22	6	5	2	3	5	9	15	3	1
Cured	3	5	5	3	4	0	0	2	2	2	0	0	0	0
Failures	0	1	1	7	12	6	4	0	1	2	7	9	3	0
No information	0	0	2	4	6	0	1	0	0	1	2	6	0	1
Minimum cure rate (per cent)	100	83	63	21	18	0	0	100	67	40	0	0	0	0

extension of the disease and prognosis (Tables 8, 9) The presence of lymph node metastases, their size and [illegible] which influenced progno[illegible] still living without evide[illegible] more than 5 years after treatment These

Table 6

Primary results, 2 to 4 months after treatment

Result	No of cases
No residual tumour found	31
Residual tumour found	9
No information	24
Total number	64

spread was detected just at completion of treatment In 2 patients who received prophylactic irradiation to the mediastinum and axillae, severe leukopenia and thrombocytopenia occurred at the end of the treatment

Results

Presentation of results In a series of African patients, presentation of the results is difficult due to follow-up problems Most patients had no personal mailing address, the address of the employer being used, as a rule Also, no official death registry existed, from which information could be obtained All patients were regularly given follow-up appointments and, if they failed to come, letters were written to the patient, the employer or to the referring hospital Results of these inquiries were, however, often negative Due to the incomplete follow-up, conventional presentation of results was impossible

The cases were classified in 3 groups those living without evidence of disease (cured), those lost track of either immediately or after an initial period of freedom from evidence of tumour (no information), and those known to be dead or to have residual or recurrent disease (failures) The quotient between the number of 'cured' and the total number of cases at risk up to a defined observation time (one and two years) represented the minimum cure rate By use of the two staging systems, it could be shown that the group no information' and the group 'failures' showed an about equally unfavourable distribution as regards anatomic extension of disease, whereas the group 'cured' represented a far less advanced population It could thus be concluded that most cases in the 'no information' group probably represented 'failures' and that the minimum cure rates must have been rather close to the true cure rates

The primary results were very promising Usually even large tumours disappeared completely or almost completely already during treatment Two to four months after completion of the treatment course, no residual tumour could be found in at least one half of the patients (Table 6)

The minimum cure rate in the total series after one year was 31 per cent and after two years 16 per cent (Table 7) A good correlation was found between the anatomic

unlikely that the prophylactic treatment added anything to the results and this method was later abandoned Of 10 one-year cured observed during the prophylactic period, 3 had only received treatment to the primary tumour site in the nasopharynx, another 4 patients had no palpable disease in the neck, while the remaining 3 cases had unilateral nodes confined to the upper part of the neck

Conclusion

Nasopharyngeal carcinoma is relatively common in the central parts of Kenya and occurs often in young people Although the cases accepted for radiation therapy were selected, these patients frequently had advanced tumours with large metastatic masses in the neck In most patients, the tumour was of the anaplastic carcinoma type

Two types of anatomic point indices are presented One and two years after the treatment the results correlated well with the indices They were good in early but poor in advanced cases, although the overall primary results, 2 to 4 months after the treatment, seemed promising Prophylactic irradiation of the mediastinum and both axillae did not improve results and was abandoned after a short trial period

Better information to the population in the regions with high incidence of nasopharyngeal carcinoma may improve survival figures Also, it is to be hoped that information about the potential benefit of radiation treatment in reasonably early cases will result in earlier referral to the department of radiation therapy

SUMMARY

Results of irradiation 1 to 3 years after treatment are presented in 64 cases of naso- ... point indices are presented

ZUSAMMENFASSUNG

Die Ergebnisse von der Bestrahlung von 64 Fallen mit Karzinom des Nasopharynx in Ost Afrika 1 bis 3 Jahre nach der Behandlung werden gegeben Zwei Typen von anatomischen Punkt Kennzeichen werden gegeben Beide sind zu den Ergebnissen gut korreliert Die prophylaktische Bestrahlung des Mediastinums und beider Axillae hatte keinen erkennbaren gunstigen Einfluss auf der Ergebnisse

RÉSUMÉ

Les auteurs présentent les résultats de l irradiation entre 1 et 3 ans après le traitement, dans 64 cas de carcinome naso pharyngien chez des Africains de l Est Ils presentent deux

Table 10

Value of prophylactic irradiation of the mediastinum and both axillae

Period	One-year cure rate	Two-year cure rate	Anatomic point indices, mean points System I	II
Non-prophylactic	10/32 (31 %)	5/32 (16 %)	2 3	4 3
Prophylactic	10/32 (31 %)	1/6 (17 %)	2 3	4 4

were, however, cases with relatively early disease without or with only small cervical nodes

A total of 35 cases were known to have died in or to live with carcinoma Of these, 15 had residual or recurrent tumour in the nasopharynx or metastases in the lymph nodes of the neck Five of these patients also had generalized disease, which was also diagnosed in another 11 patients A total of 16 patients were thus known to have developed generalization within the first three years after treatment The real number may be assumed to have been higher as follow-up data were lacking in several patients The distant metastases occured in the following sites lymph nodes (outside neck) 5 cases, bone 7 cases, lung 2 cases, subcutaneous tissue 2 cases, pleura, liver and central nervous system 1 case each

At the time for this analysis, 19 patients were known to be alive and were seen in the follow-up clinic from October 1971 to February 1972 Of these, 13 were without evidence of tumour for observation times varying from 14 to 38 months Six lived with malignancy for observation times from 13 to 33 months

Prophylactic irradiation of the mediastinum and the axillae was given to patients treated after October 21, 1969 The dose to these targets was about 4 000 rad in about 4 weeks and this treatment was given simultaneously with the irradiation of the primary tumour and the neck A total of 36 patients did not receive prophylactic irradiation and the one-year minimum cure rate in this series was 13/36 (36 per cent) Prophylactic treatment was given to 28 patients and the one-year minimum cure rate in this group was 7/28 (25 per cent) This comparison is, however, unfair in that a few patients did not receive prophylactic irradiation even after October 1969 being prognostically favourable It would appear more correct to compare all cases treated during the non-prophylactic period with all cases treated during the prophylactic period When both these groups were compared (Table 10), no difference was found between the one- and two-year minimum cure rates The groups were too small for statistical evaluation and may, furthermore, not have been entirely comparable, although the mean point value in the prognostic index based on the anatomic extension of the tumour was the same for both groups (Table 10) However, it seems

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LOCAL PROGNOSIS AFTER COMBINED EXTERNAL AND INTERSTITIAL RADIATION THERAPY FOR CARCINOMA OF THE TONGUE

T INOUE, H FUCHIHATA, T WADA and Y SHIGEMATSU

Interstitial radiation therapy for the primary lesion and radical neck dissection for the metastatic nodal disease is in this department regarded as the treatment of choice for carcinoma of the tongue Since the treatment results were not sufficiently good except in early malignancy, combined external and interstitial irradiation of the primary site has been used for the past 10 years The external irradiation included the [illegible]

[illegible] also applied in a small number of cases (FUCHIHATA et coll 1974)

The reason for the adjunctive use of external therapy was mainly to decrease the tumor size in order to facilitate the insertion of the radium needles, and to prevent the development of nodal metastases MAKINO (1973) demonstrated that the adjunctive use of external irradiation resulted in delayed development of nodal metastases without significant [illegible] pared with pa[illegible] control of the [illegible] to be analysed

The local prognosis of carcinoma of the tongue treated with interstitial radium

Submitted for publication 15 January 1976

types d'indice anatomique par points. Ces deux indices ont une bonne corrélation avec les résultats. L'irradiation prophylactique du médiastin et des aisselles n'amène pas d'amélioration évidente des résultats.

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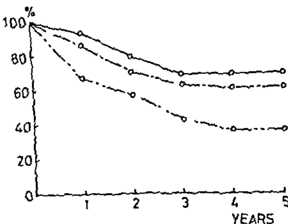


Fig 1 Actuarial survival curves for 114 patients with carcinoma of the tongue by T classification ——, T1 (28), —·—, T2 (64), —··—, T3 (22)

The T1N0 cases were given 70 Gy (7 000 rad) with interstitial irradiation alone, T2N0 and T3N0 cases received 30 Gy (3 000 rad) in 10 fractions over 2 weeks with telecobalt therapy and after a gap of 10 days (70 Gy) was given with interstitial therapy In case of lymphadenopathy (N1 and N2), a radical neck dissection was performed following the completion of the scheduled irradiation Patients with a far advanced lesion or with a fixed node (N3) were treated on an individual basis, irradiation, surgery, chemotherapy, etc

Interstitial therapy only was given to 41 patients (26 of T1, 14 of T2, and one of T3), 73 patients were treated with telecobalt therapy followed by interstitial therapy (2 of T1, 50 of T2, and 21 of T3)

Results

The overall actuarial survival rates were 84, 60 and 58 per cent after 1, 3 and 5 years In spite of the high cure rate in T1 and T2 cases (68 and 60 per cent 5-year survival rates), the 5-year survival rate in T3

Two year disease free rates appear in

interstitial irradiation were excluded

malignancy, 2 of an unknown disease, and one was lost to the follow-up within 2 years) Two year disease free rate means no evidence of local recurrence, nodal disease or distant metastasis within 24 months after the initial treatment Two-year local recurrence free rates appear in Table 3, in which 21 cases were excluded (9 died of neck node metastases, 4 of distant metastasis, 4 of intercurrent disease, one of other malignancy, 2 of an unknown disease, and one was lost to the follow-up within 2 years Two-year local recurrence free rate means no evidence of local recurrence within 24 months after the treatment of the primary lesion

An analysis was made of the local condition of the irradiated area and correlated

Table 1

TNM classification of 114 patients with previously unirradiated carcinoma of the tongue treated with interstitial irradiation with or without additional telecobalt therapy

	N0	N1	N2	N3	Total
T1	25	3	—	—	28
T2	47	16	—	1	64
T3	11	8	1	2	22
Total	83	27	1	3	114

Table 2

Two-year disease free rates

	N0	N1	N2	N3	Total
T1	12/22	1/3	—	—	13/25
T2	24/45	3/15	—	0/1	27/61
T3	5/11	1/6	1/1	0/2	7/20
Total	41/78	5/24	1/1	0/3	47/106

Table 3

Two year local recurrence free rates

	N0	N1	N2	N3	Total
T1	18/21	2/3	—	—	20/24
T2	32/41	2/9	—	—	34/50
T3	7/11	1/5	1/1	0/2	9/19
Total	57/73	5/17	1/1	0/2	63/93

application with or without additional telecobalt therapy is now analysed using TDF (Time-Dose-Fractionation) factors proposed by ORTON & ELLIS (1973) and ORTON (1974)

Material and Methods

From 1968 through 1972 168 patients with carcinoma of the tongue were registered Of these, 114 patients were treated with interstitial therapy with or without additional external irradiation The patients were staged retrospectively according to the TNM system proposed by the UICC (1973) 28 cases belonged to stage T1, 64 to T2, and 22 cases to stage T3, 83 cases were N0, 27 cases N1, one case N2, and 3 cases N3 (Table 1)

dose of interstitial therapy should be adjusted depending on the dose rate. Since the biologic equivalent dose was derived from the tissue tolerance, the physical standard dose could vary within a wide range. Recently, PIERQUIN et coll. (1973) reported that the tolerance of the oral cavity tissue was not so much influenced by the dose rate. This statement was based on their many cases treated with ^{192}Ir wires with various dose rates. They concluded that adjustments of the dose to overall time, which has sometimes been suggested in order to compensate for supposed differences in biologic effect, were unnecessary.

GILBERT et coll. (1975) obtained good results with external radiation therapy alone, but they also reported that osteonecrosis occurred in 13 per cent of the patients. VERMUND & GOLLIN (1973) reported that only 5 of 112 patients developed local necrosis following irradiation. In the present material the survival rate was high, but the frequency of local necrosis was also high (23 of 93 patients). Adjunctive use of external irradiation to interstitial therapy with the dosage used does not seem to be an adequate method for controlling the primary carcinoma of the tongue. On the contrary, additive use of external irradiation resulted in a high risk of bone necrosis.

SUMMARY

Of 36 patients with early carcinoma of the tongue treated with [illegible]
were controlled, 10 recurred and [illegible]
with telecobalt therapy followed [illegible]
and 22 developed local necrosis [illegible]
tion was unacceptably high. Interstitial therapy alone may be a more adequate method for the primary tumour.

ZUSAMMENFASSUNG

Von 36 Patienten, die wegen eines frühen Zungenkarzinoms interstitielle Bestrahlung erhielten, wurden 25 kontrolliert, in 10 trat ein Rezidiv auf und in einem eine lokale Nekrose. Von 57 Patienten mit fortgeschrittenen Tumoren, mit Telecobalttherapie und interstitielle Bestrahlung behandelt, wurden 15 kontrolliert, in 20 trat ein Rezidiv auf und in 22 eine lokale Nekrose. Die Nekrosenfrequenz nach kombinierter Bestrahlung ist zu hoch um akzeptiert werden zu können. Die interstitielle Bestrahlung scheint eine bessere Methode für die Behandlung der Primärgeschwulst zu sein.

RÉSUMÉ

Sur 36 malades traités pour un cancer de la langue au début par irradiation interstitielle, 25 ont été guéris, 10 ont récidivé et un a présenté une nécrose locale. Sur 57 cas avancés traités par télécobalthérapie suivie d'irradiation interstitielle, 15 ont été guéris, 20 ont récidivé et 22 ont présenté une nécrose locale. La nécrose après irradiation combinée se produit avec une fréquence inacceptable. Il se pourrait que la thérapie interstitielle seule soit une méthode plus appropriée pour le traitement de la tumeur primitive.

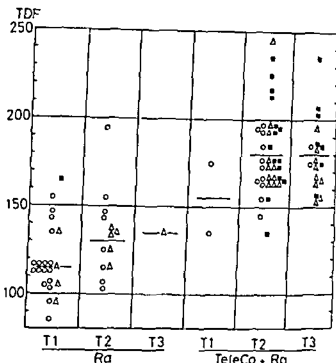


Fig 2 Local prognosis for 93 patients with carcinoma of the tongue related to treatment method, size of tumour and TDF factors o, Control, △, recurrence, ■, necrosis

with the TDF values (Fig 2) In the interstitial irradiation group muscular necrosis occurred in one patient only, while osteonecrosis developed in 22 patients in the group which received combined external and interstitial irradiation The most common site for necrosis was the mandible, with clinical bone exposure and bone necrosis on radiography These necroses healed spontaneously within 3 years while the muscular necrosis remained for more than 6 months The necroses had no influence on the mortality Average values of the TDF are 115, 130 and 135 for T1, T2 and T3, respectively, treated with interstitial therapy, and 155, 180 and 180 for T1, T2 and T3, respectively, given telecobalt and interstitial irradiation The great *majority of the necroses occurred after TDF values above 160 The frequency of* local recurrence did not correlate so well with the TDF values

Discussion

The effect of high dose rate fractionated therapy and low dose rate continuous *interstitial irradiation may be assessed by three calculation systems, viz* the Cell population kinetic system (COHEN 1972), the Cumulative radiation effect (KIRK et coll 1971, 1972, 1973, 1975), and the Time-dose-fractionation factors (ORTON & ELLIS 1973, 1974, ORTON 1974) *In this analysis, the local prognosis was estimated* using TDF factors The dose rate factor is of interest both to the therapist and the biologist (HALL 1972) From the practical point of view of the therapist, the biologic equivalent dose of the *interstitial therapy was derived from clinical experience by* PATERSON (1963) His standard dose was 6 000 rad in 7 days He mentioned that a

dose of interstitial therapy should be adjusted depending on the dose rate Since the biologic equivalent dose was derived from the tissue tolerance, the physical standard dose could vary within a wide range Recently, PIERQUIN et coll (1973) reported that the tolerance of the oral cavity tissue was not so much influenced by the dose rate This statement was based on their many cases treated with ^{192}Ir wires with various dose rates They concluded that adjustments of the dose to overall time, which has sometimes been suggested in order to compensate for supposed differences in biologic effect, were unnecessary

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SUMMARY

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Von 36 Patienten die wegen eines fruhen Zungenkarzinoms interstitielle Bestrahlung erhielten wurden 25 kontrolliert in 10 trat ein Rezidiv auf und in einem eine lokale Nekrose Von 57 Patienten mit fortgeschrittenen Tumoren mit Telecobalttherapie und interstitielle Bestrahlung behandel[illegible] in 22 eine lokale Nekrose Die [illegible] hoch um akzeptiert werden zu [illegible] Methode fur die Behandlung de[illegible] geschwulst zu sein

RÉSUMÉ

Sur 36 malades traités pour un cancer de la langue au debut par irradiation interstitielle, 25 ont été guéris 10 ont recidivé et un a présenté une nécrose locale Sur 57 cas avancés traités par télécobalthérapie suivie d irradiation interstitielle 15 ont été guéris, 20 ont récidivé et 22 ont présenté une nécrose locale La nécrose après irradiation combinée se produit avec une fréquence inacceptable Il se pourrait que la thérapie interstitielle seule soit une méthode plus appropriée pour le traitement de la tumeur primitive

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DIAGNOSTIC VALUE OF GALLIUM-67 IN MALIGNANT LYMPHOMA

H.-B. MAKOSKI, H.-J. TESKE and G. BECKER

Exact knowledge of the extent of a disease is a prerequisite for successful treatment. This is exemplified by the encouraging results in the treatment of Hodgkin's disease and of so-called non Hodgkin's lymphoma during recent years. Radiography including lymphangiography, laboratory tests, scintigraphy of skeleton, spleen and liver, exploratory laparotomy with biopsy of liver and lymph nodes have been included for staging of these diseases (Rye and Ann Arbor Conferences).

In 1969 EDWARDS & HAYES reported on tumour demonstration using ^{67}Ga scanning and later TURNER et coll. (1972) and PALUMBO et coll. (1974) reported a correct localization up to 79 per cent of the lesions in Hodgkin's disease.

After intravenous injection, carrier free gallium-citrate binds with transferrin and accumulates in the kidney, liver, spleen and skeleton. It is excreted mainly by urine and stools. At 48 to 72 hours after the injection, the activity is low in plasma and normal tissue and relatively high in neoplastic lesions.

Recently the mechanism of uptake of ^{67}Ga in neoplasms of the soft tissue and in lymphomas was demonstrated. The nuclide is bound to proteins. In subcellular distribution, ^{67}Ga is located in the crude nuclei fraction of Hodgkin's granuloma and in anaplastic carcinoma. Generally, the uptake of ^{67}Ga is significantly higher in

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Table 2

Comparison of ^{67}Ga results with confirmed sites of disease

	Neck	Mediastinum	Para aortic mesenteric region	Iliac lymph nodes	Inguinal lymph nodes	Spleen	Other sites	Total
Hodgkin's disease, not treated								
Involved	5	6	12	10	6		3	42
Correct	3	6	8	8	3		3	31
False negative	2		4	2	3			11
False positive	1	1	2	5	2	1		12
Hodgkin's disease, treated								
Involved		7	5	3	1	1	5	22
Correct		5	3	3	1	1	4	17
False negative		2	2				1	5
False positive			1	1	1			3

were examined in the same manner (M and T) Enlarged lymph nodes in the cervical, axillary and inguinal regions were documented by physical examination only

Carrier free ^{67}Ga citrate prepared by Philips-Duphar was injected intravenously 72 hours before scanning in a dose of 1 3 to 2 mCi in a volume up to 2 ml Scans were performed on a rectilinear scanner (Scintimat 2, Siemens) with a 12 5 cm × 5 cm detector and a multihole collimator Patients were scanned from head to chest and from abdomen to thighs Simultaneous anterior and posterior scans were made with the patients supine Laxatives and cleansing enemas were given for two days to remove active gallium from the colon

Results

The results are presented in Tables 1 to 5 In 63 per cent of the untreated patients with Hodgkin's disease, the usual staging procedures and ^{67}Ga scanning gave similar results, at scanning additional information was obtained in 16 per cent on sites which cannot be examined at radiography but only at physical examination In this group there were 26 per cent false positive and 11 per cent false negative scans

Only 50 per cent of previously treated patients with Hodgkin's disease had a correct diagnosis on ^{67}Ga scanning despite the fact that recurrent disease was suggested In one case additional information was obtained at scintigraphy against clinical examination and radiography In 4 of 8 patients of this group, ^{67}Ga scans did not reveal any evidence of disease, in 2 cases paraaortic involvement could not be detected

Table 1

^{67}Ga scintigraphy of 58 patients. Results in per cent

	Scintigraphy radiography	Scintigraphy				
		Additional information	Correct	False positive	False negative	Total false diagnoses
Hodgkin's disease						
not treated	47	16	63	26	11	37
treated	38	12	50		50	50
Non Hodgkin's disease						
not treated	21	26	47	42	11	53
treated	25	8	33	42	25	67

Hodgkin's granuloma and reticulum cell sarcoma than in most other tumours (CLAUSEN et coll. 1974).

Primarily, ^{67}Ga binds with the plasma membranes of human T-lymphocytes (MERZ et coll. 1974). At electron microscopy it has been demonstrated that ^{67}Ga associates with lysosomes both in murine leukemia and in hepatoma in the rat. These findings reveal the basic mechanism of the affinity of ^{67}Ga to tumours, abscesses and inflammatory processes.

In a material of 100 untreated patients with non-Hodgkin's lymphoma, 64 per cent had microscopically documented extranodal disease, whereas only 13 per cent had regional involvement. This implied a treatment different from that used in Hodgkin's disease (JOHNSON et coll. 1974).

Material and Method

Fifty-eight patients with microscopically verified Hodgkin's disease or non Hodgkin's lymphoma were subjected to scanning with ^{67}Ga-citrate in the period from December 1970 to July 1974. Thirty eight patients were previously untreated (19 with Hodgkin's disease, 12 with lymphosarcoma and 7 with reticulum cell sarcoma). Twenty patients with possible recurrent disease after chemotherapy, irradiation or combined therapy were included as a separate group (eight with Hodgkin's disease, twelve with non-Hodgkin's lymphoma).

Exploratory laparotomy was performed in the patients with untreated Hodgkin's disease and also in selected cases with non-Hodgkin's lymphoma. Chest films, with tomography in the presence of lesions, and bilateral lymphangiography were obtained in each case.

The scans were evaluated by two of the authors (M. and B.) without knowledge of the patient's identity, clinical history or the results of other examinations. Films

Table 4

Comparison of ^{67}Ga and radiography. Results in per cent

	^{67}Ga and radiography correct		^{67}Ga			Radiography, no information ^{67}Ga positive
	Positive	Negative	False positive	False negative	No information	
Hodgkin's disease not treated						
Thorax	37	58	5			
Abdomen	47	11	21	11	10	
Hodgkin's disease treated						
Thorax	75	12.5		12.5		
Abdomen	25	25	37.5			12.5
Non Hodgkin's lymphoma not treated						
Thorax	10	74	16			
Abdomen	53	11	26		10	
Non Hodgkin's lymphoma treated						
Thorax	25	59	8		8	
Abdomen	8	8	34	25	8	17

Similar results were obtained in treated patients with reticulum cell sarcoma and lymphosarcoma.

The comparison of ^{67}Ga scan with conventional radiography reveals a good correlation of involvement in the chest but a high ratio of false scans was encountered in the retroperitoneal mesenteric regions, especially in treated patients (Table 5).

Discussion

Physiologic reasons exist for the application of ^{67}Ga in staging procedures of patients with lymphoma. The absorbed dose is low: total body dose 0.34 rad/mCi ^{67}Ga citrate injected intravenously, gonadal dose 0.21 rad/mCi, testes and bone tissue 0.64 rad/mCi, bone marrow 0.53 to 0.78 rad/mCi. No special radiation protection is necessary (half life 79.9 h). γ-energy 42 per cent at 0.092 MeV, 24 per cent at 0.182 MeV, 22 per cent at 0.3 MeV and 7 per cent at 0.388 MeV, intestinal excretion 10 to 15 per cent, renal excretion 20 to 30 per cent.

Extremely good preparation of the bowel is necessary to avoid disturbance of the images by superimposed activity. Furthermore, it is impossible to differentiate inflammatory lesions from neoplastic ones. In the reports of TURNER et coll. and of PALUMBO et coll. patients having received chemotherapy or radiation therapy were

Table 3

Comparison of ^{67}Ga results with confirmed sites of disease

	Neck	Mediastinum	Para-aortic mesenteric region	Iliac lymph nodes	Inguinal lymph nodes	Spleen	Other sites	Total
Non Hodgkin s disease not treated								
Involved	5	2	6	7	5		6	31
Correct	4	1	6	7	5		5	28
False negative	1	1					1	3
False positive	1	1	2	3	1		2	10
Non Hodgkin s disease treated								
Involved	2	2	3	4	3		3	17
Correct	1	2		1	2		1	7
False negative	1		3	3	1		2	10
False positive			3	1		1		5

by clinical or radiologic means but by operation only In one patient with some positive findings on scanning no pathologic paraaortic or iliac lymph nodes were demonstrated however laparotomy and lymph node dissection revealed lympho granulomatous tissue in these regions

In non Hodgkin s lymphoma there was less correlation between radiography clinical findings and gallium scanning false positive results prevail (Table 1)

By comparing ^{67}Ga scans with the results of clinical examination and radiography (Tables 2 to 4) more regions were found to be involved at scanning No correlation existed between the number of patients correctly diagnosed and the number of sites correctly detected Detailed information on the sites mainly involved by lymphoma is presented in these tables

Most of the false negative findings in Hodgkin s disease were due to failure in identifying tumour activity in paraaortic mesenteric regions On the other hand activity in these sites accounts for the high rate of positive results altogether 29 per cent This was due to superimposed activity within the gut even though cleansing enemas had been given Additional information as compared with conventional radiography was found in the neck axilla and supraclavicular fossa (16 per cent) In treated patients with Hodgkin s disease there was additional evidence of disease in the splenic region

In untreated patients with non Hodgkin s disease one false negative result occurred in a case with mediastinal lymphoma False positive involvement was again displayed in the retroperitoneal lymph nodes In two cases inflammatory disease was diagnosed in one patient activity accumulated in the laparotomy scar 7 months after operation

^{67}Ga scanning seems to be a supplementary procedure in the staging of lymphoma It may give additional information to radiography including lymphangiography In case of contraindication to lymphangiography, ^{67}Ga scintigraphy offers a possibility to evaluate retroperitoneal lymph nodes and other sites apart from the chest Even in patients with groin dissection and discontinuity of lymph vessels, information about iliac lymph nodes may be obtained, involvement of regions not possible to examine by radiography may be revealed

Our general attitude towards staging procedures of patients with non-Hodgkin's lymphoma is not much different from that presented by JOHNSON et coll, who reported a high rate (64 per cent) of extranodal involvement at an early stage The treatment planning is influenced by this situation

SUMMARY

The results of lymphangiography and other radiologic procedures are compared with those obtained by ^{67}Ga scintigraphy in staging of 27 patients with Hodgkin's disease and 31 patients with non Hodgkin's lymphoma A high degree of correlation was found between lymphangiography and ^{67}Ga scintigraphy Exact localization, however, was only possible by lymphangiography In some cases, the extent of disease found on scanning appeared to be smaller compared to radiography Within the chest ^{67}Ga scintigraphy and conventional radiography give almost similar results Differentiation between neoplastic and inflammatory lymph node involvement is impossible

ZUSAMMENFASSUNG

Bei 27 Patienten mit Hodgkin scher Erkrankung und 31 Patienten mit Non Hodgkin Lymphomen
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und c ... Resultate Eine Unterscheidung zwischen Tumorbefall und entzundlichen Veranderungen lässt sich nicht treffen

RÉSUMÉ

Les auteurs comparent les resultats de la lymph
... la lima ... ques ... les atteintes

Table 5

^{67}Ga scintigraphy in Hodgkin's disease, untreated cases

	PALUMBO et coll	TURNER et coll	*Present series*
Number of patients	23	20	19
Scint./clin. findings	*61%*	*60%*	63%
Additional information			
at scanning	No data		
Correct		25%	16%
False negative		*15%*	10%
Sites			
Correct		*79%*	74%
False positive	26%	20%	26%
False negative	*13%*	*20%*	11%

eliminated because of inconsistent imaging of the treated lymph nodes. Yet, it is essential for satisfactory treatment result to diagnose recurrent disease at an early stage. Thus, in the present series treated patients have been included as well.

All patients were reexamined. *Laparotomy could rarely be performed in previously* treated patients but involvement of mediastinum and hilum was controlled by conventional films (sometimes also by tomography). Physical examination was used as a reference for neck, axillary and supraclavicular fossae. Two of 5 involved sites could not be evaluated by ^{67}Ga.

The group of untreated patients with Hodgkin's disease may be compared with *the reports published (Table 5). Compared to radiography,* additional evidence of *disease in head and neck was gained by nuclide scanning in 16 per cent in the present material against 25 per cent* by TURNER et coll. Nevertheless false negative cases existed, PALUMBO et coll.: 2 in the paraaortic-mesenteric region and 2 in the spleen, TURNER et coll.: 3 in the neck, 1 in the paraaortic-mesenteric region and 2 in the iliac *lymph nodes, present series: 2 in the neck, 4 in the paraaortic-mesenteric region* 2 in the iliac lymph nodes and 3 in the inguinal lymph nodes.

False positive scans prevailed in some regions, PALUMBO et coll. reported more *false positive results for the mediastinum (5 against 2 paraaortic-mesenteric and 1* spleen), whereas TURNER et coll. presented almost the same number of false positive scans *(20 per cent) as in the present series (26 per cent),* i.e. *1* mediastinum (against 1 paraaortic-mesenteric, 1 inguinal and 3 spleen), compared to 29 confirmed locations against one false positive mediastinal *involvement of 12 false positive sites in 42* confirmed sites (1 mediastinal, 1 neck, 2 paraaortic-mesenteric, 5 iliac, 2 inguinal and 1 spleen). On the other hand, in accordance with TURNER et coll. in the present *material most often* the false positive scans were found in the abdominal region. The rate of correct identification of all sites was 79 per cent against 74 per cent, respectively. *From the report of PALUMBO et coll. no definite data can* be obtained

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PULMONARY CONTRACTION FOLLOWING ^{60}CO IRRADIATION OF MAMMARY CARCINOMA

T OPPEDAL and A KOLBENSTVEDT

Chest films following irradiation of mammary carcinoma often reveal a poorly defined, fan shaped infiltration of the lung parenchyma radiating from the hilum and appearing from a few weeks to a few months after the end of treatment The process is that of an irradiation pneumonitis, and is followed by gradual contraction of the involved parenchyma and displacement towards the mediastinum (HAGEN & KOLBENSTVEDT 1972) The end result is a fibrosis along the border of the mediastinum, easily overlooked and thus the chest films may give the false impression of resolution and disappearance of the radiation induced abnormalities Elevation of the hilum and diaphragm, and a shift of the mediastinum towards the affected side have been mentioned in the literature as signs of pulmonary retraction following radiation therapy (MCINTOSH & SPITZ 1939, ROSS 1956, LOUGHEED & MAGUIRE 1960) Less attention has been given to the concomitant elevation of the right superior interlobar fissure which also constitutes a useful anatomic indicator of the degree of contraction (Fig 3)

The ventilatory function and the pulmonary gas exchange have been analyzed (HÖST & VALE 1973) and the pulmonary circulation (NOTTER et coll 1970) has been investigated by use of isotopes from 6 to 14 months after radiation therapy However, this may not reflect the final pulmonary impairment if the contraction proceeds during a longer period of time

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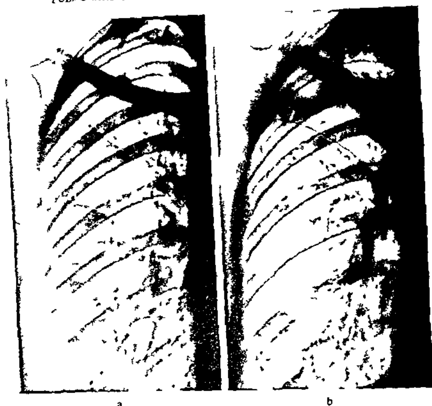


Fig 3 Right lung a) Before treatment Arrows indicate interlobar fissure b) 26 months after postoperative irradiation with ^{60}Co Contraction of the upper lobe with displacement upwards of the interlobar fissure and secondary distension of the lower lobe

On re examination of the films the right superior interlobar fissure was outlined with a marker On top of the pre-treatment film, the later films were placed one by one and the upward displacement of the interlobar fissure was measured as indicated in Fig 2 The compatibility of the films with regard to the same phase of inspiration was checked by the position of the unaffected left hemidiaphragm

The height and weight of the patient and the height of the upper treatment field was noted and the a p diameter of the thorax was measured on lateral films along the shortest line through the hilum including the extrathoracic soft tissues

Results

Upward displacement of the interlobar fissure was the only sign of irradiation-induced pulmonary contraction in 7 of the 38 patients The maximum elevation was 11 5 cm the minimum was 0 5 cm Nearly two thirds of the patients had a maximum

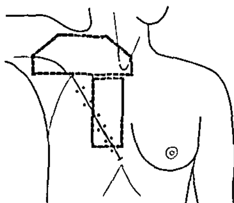


Fig 1

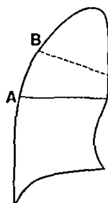


Fig 2

Fig 1 Treatment fields in postoperative ^{60}Co irradiation for mammary carcinoma stages I and II

Fig 2 Diagram of interlobar fissure displacement The distance between intersection point A (before treatment) and B (after treatment) was measured

Therefore it seemed of interest to elucidate the extent and duration of pulmonary contraction as indicated by elevation of the right superior interlobar fissure during a period of at least 4 years following irradiation, and to obtain information about a possible reversibility of the abnormalities as suggested by BATE & GUTTMANN (1957) The degree of contraction was also correlated to age, weight and height of the patient, depth of the chest and the size of the irradiation fields

Material and Methods

During the years 1968 through 1972, a total of 72 patients with carcinoma of the right breast, stages I and II, were treated by radical mastectomy followed by ^{60}Co irradiation Patients with carcinoma of the left breast were not included in the series, as no similar interlobar fissure exists on this side Two adjacent fields were irradiated, the upper field was inclined 15° laterally to avoid the deeper midline structures, its medial border being 1 cm to the left side of the midline, that of the lower field was at the midline, the border between the two fields was located 1 cm below the jugular notch (Fig 1) Each field received 57 Gy (5 700 rad) in 20 fractions over a period varying between 26 and 40 days

Because the right superior interlobar fissure was not visible in the pre-treatment films, 19 patients were excluded An additional 15 patients were excluded due to absence of follow-up films for a minimum of 4 years after treatment 8 of these because of too short a survival There remained 38 patients fulfilling the criteria One patient was aged between 30 and 39, 7 between 40 and 49, 17 between 50 and 59, and 13 between 60 and 69 years Chest radiography was performed in all patients before and immediately after the treatment Over a 4-year period the total number of these follow-up films was 179 with a range of 1 to 11 films per patient

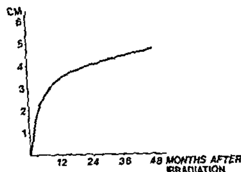


Fig 5 Average post irradiation pulmonary contraction as measured by displacement upwards of the interlobar fissure (38 patients)

which varied from 7 5 to 11 cm The antero-posterior thoracic diameter varied from 22 to 32 cm No difference in the degree of retraction of the lobe was found between patients with deep and narrow chests

Discussion

In a previous, similar series of 70 patients, post irradiation abnormalities were observed in 61, i e 87 per cent (HAGEN & KOLBENSTVEDT) The elevation of the interlobar fissure was not registered in that series, which included patients irradiated on the left side In the present group, all patients were irradiated on the right side and special attention was given to the interlobar fissure Contraction of the right upper lobe was observed in all patients

Most of the contraction of the lobe occurred within one year after treatment, but the process continued through the entire observation period This implies that analyses of the pulmonary function one year after treatment probably do not reveal the final pulmonary impairment

The upward displacement of the interlobar fissure cannot be related to the ipsilateral surgery Similar changes have not been observed after radical mastectomy without postoperative irradiation, but they have been encountered in non operated patients following mantle field irradiation

Small differences in the phase of inspiration when the films were exposed, as estimated by the position of the unaffected left hemidiaphragm, produced no noticeable effect on the site of the [illegible]

The reason why [illegible]
occur, remains obs [illegible] with a narrow chest might have more lung tissue irradiated and therefore be liable to more severe contraction However, this theory was not confirmed in the present material MCINTOSH & SPITZ stated that

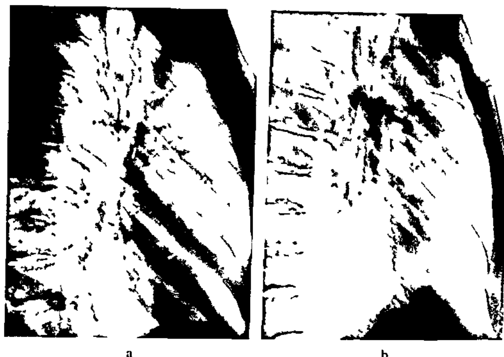


Fig. 4. a) Before treatment. Arrows indicate interlobar fissures. b) 14 months after post operative irradiation with ^{60}Co. Contraction of upper lobe with displacement upwards of both interlobar fissures. Secondary distension of the lower and middle lobes.

displacement of the interlobar fissure between 2 and 6 cm (Table). The contraction of the upper lobe led to a compensatory distension of the lower and middle lobes (Figs. 3 and 4). The position of the interlobar fissure was more clearly visible in p.a. than lateral films, although occasionally well demonstrated in the latter (Fig. 4). The average elevation of the interlobar fissure in the 38 patients appears in Fig. 5, which reveals that 50 per cent of the displacement of the fissure occurred within *4½ months and 75 per cent within 14½ months after the end of treatment. Contraction* of the lobe continued at a diminishing rate during the remaining observation period (Fig. 6). The maximum elevation observed during the last two years was 1.5 cm. No downward displacement of the interlobar fissure indicating reversal of contraction was noticed.

No statistically significant correlation was found between contraction and age, weight or height of the patients. Neither was any significant correlation found between the extent of the elevation of the fissure and the height of the upper treatment field,

Table

Maximum displacement upwards of the interlobar fissure

Displacement (cm)	0–1.9	2.0–3.9	4.0–5.9	6.0–7.9	8.0–9.9	10.0–11.9
No. of patients	4	11	13	4	3	3

the lungs of elderly subjects with arterio sclerosis were especially prone to radiation pneumonitis and permanent fibrosis HAGEN & KOLBENSTVEDT reported a higher frequency of marked post irradiation abnormalities in the older age groups as estimated by the extent of pulmonary infiltration In the present series, the degree of pulmonary contraction was practically the same in all age groups

As the symptoms of radiation fibrosis are usually modest and the final roentgenologic findings may be inconspicuous unless the films are scrutinized for signs of contraction of the upper lobe, the pulmonary injury seems to have received insufficient attention in the planning of radiation treatment Three patients of the present series had contraction with elevation of the interlobar fissure of more than 10 cm and a corresponding compensatory distension of the lower and middle lobes This fact deserves careful consideration when the treatment principles of mammary carcinoma are considered

SUMMARY

Pulmonary contraction as measured by elevation of the right superior interlobar fissure was investigated in 38 patients with carcinoma of the right breast treated by radical mastectomy followed by irradiation with ^{60}Co Contraction of the right upper lobe was observed to extend over a minimum of four years although at a diminishing rate

ZUSAMMENFASSUNG

Bei 38 Patienten die wegen rechtseitigen Mammakarzinom mit radikaler Mammaamputation und ^{60}Co-Bestrahlung behandelt wurden waren wurde die Lungenschrumpfung nach der Aufziehung der Fissura interlobaris superior beurteilt Schrumpfung des rechten oberen Lungenlappens wurde mindestens vier Jahre beobachtet obwohl im abnehmenden Masse

RESUMÉ

Les auteurs ont examiné sur 38 malades atteintes de cancer du sein droit traitees par mammectomies radicales suivies d irradiation par le ^{60}Co la retraction pulmonaire mesuree par l élevation de la scissure interlobaire superieure droite Ils ont constaté que la retraction du lobe supérieur droit s etend sur un minimum de 4 ans bien qu elle aille en diminuant

REFERENCES

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LOUGHEED M N and MAGUIRE G H Irradiation pneumonitis in the treatment of carcinoma of the breast J Canad Ass Radiol 11 (1960) 1



a



b



c

Fig (Right lun a) Before treatment Arrows ind cate interlobar fissure b) 2 years after treatment Contraction of right upper lobe with interlobar fissure elevat on has occurred c) 3½ years after treatment Further contraction has occurred as judged by the pos tion of the interlobar fissure

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RÉSUME

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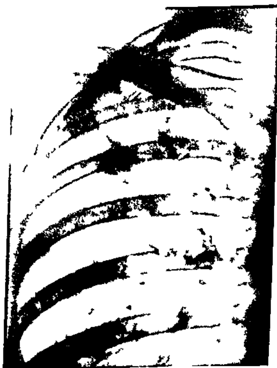
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a



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Les auteurs ont examiné sur 38 malades atteintes de cancer du sein droit traitées par mammectomies radicales suivies d'irradiation par le ⁶⁰Co la rétraction pulmonaire mesurée par l'élévation de la scissure interlobaire supérieure droite. Ils ont constaté que la rétraction du lobe supérieur droit s'étend sur un minimum de 4 ans bien qu'elle aille en diminuant.

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FROM THE RADIUMCENTER, FINSENINSTITUTET, STRANDBOULEVARDEN 49, DK-2100 COPENHAGEN, DENMARK.

SINGLE-DOSE IRRADIATION OF BONE METASTASES

N.-H. JENSEN and K. ROESDAHL

Single-dose irradiation has been reported to be a useful tool in the management of widespread metastatic disease (DELCLOS & JOHNSON 1964, VARGHA et coll. 1969, FLETCHER 1973).

For a period of 4 months this mode of approach was applied to 64 patients with painful, radiographically verified bone metastases. Patients with imminent fracture through the metastasis were excluded. Sixty-six of the lesions were osteolytic, 30 osteosclerotic and 8 mixed.

Of a total of 104 irradiations, 84 were given with high energy photons (mainly ^{60}Co), while 200 kV roentgen radiation was applied in 16 and betatron electrons in 4. In 54 of the 64 patients the primary tumour was carcinoma of the breast, in the remaining 10 cases carcinoma of the prostate, the kidney or the thyroid. Of the total material 8 patients (12 per cent) were less than 50 years old, 16 (25 per cent) between 50 and 60, 19 (30 per cent) between 60 and 70, and the remaining 21 (33 per cent) more than 70 years old. The calculated tumour doses appear in the Table.

The maximum tumour dose was 7.46 Gy (746 rad), the minimum 3.02 Gy (302 rad). Field sizes varied between 32 and 400 cm², 15 per cent were larger than 200 cm² and 15 per cent smaller than 80 cm². There was a marked tendency towards reciprocal connection between the dose given and the field size.

The follow-up period after treatment varied between 2 weeks and 15 months with

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Table
Tumour dose in single dose treatments

Tumour dose (Gy)	No of treatments
<4	5
4–5	21
5–6	34
6–7	34
>7	10
Total	104

46 per cent of the patients exhibiting a follow-up time of more than 6 months, and 23 per cent of more than 12 months Within 4 months following treatment 49 per cent of the patients were dead

Results and Discussion

All patients were seen in the out-patient clinic 2 weeks after treatment for assessment of response, skin reaction and other side effects Later examinations were performed in 2 to 4 weeks interval, depending on the general condition None failed to report

The response was classified into 3 groups (1) free of pain all symptoms from the irradiated bone metastases disappeared, and no further need for analgesics, (2) improvement pain diminished and reduction of analgesics, and (3) no effect

Two weeks following treatment 25 per cent (26 patients) presented without pain and 54 per cent (56) had improved, no effect was encountered in 21 per cent (22 patients) When last seen 15 per cent (16 patients) had still pains, while 23 per cent (24) indicated relief and 62 per cent (64 patients) were free of pain

No difference in response rate existed between long-time and short-time survivors

No correlation between dose and response was found, thus the results corresponded to those of VARGHA et coll Furthermore no relationship existed neither between the microscopic type of the primary tumour and the response to single-dose treatment nor between age and effect

Retreatment (5 irradiations/week) to previously irradiated areas was given to 6 patients, of whom 5 responded well with no side effects Systemic reactions occurred in one instance (nausea after pelvic irradiation to a field measuring 400 cm², the tumour dose amounting to 6 15 Gy (615 rad) The inconvenience disappeared in a few days

Twenty-nine patients received single-dose irradiation of more than one area It appeared that if a good response was obtained in one site, the same effect could be expected in another site with the same dose Erythema developed in 8 of 16 irradia-

tions with roentgen rays, in 6 of 84 with high energy photons and in 2 of 4 treatments with electrons In no case a moist reaction occurred

Adjuvant hormone therapy was given to 64 per cent of the patients: the majority were treated with androgens Non-hormone chemotherapy was administered to 5 patients during the follow-up period because of further dissemination, all were and remained pain-free in the previously treated areas No difference as regards single-dose response was established between the androgen-treated and the non hormone-treated groups The single-dose therapy was not administered to hormone-treated patients as long as they were free of pains with this therapy

The follow-up time is rather short, but the preliminary results seem to indicate that in the majority of patients with bone metastases from a malignant tumour, a single exposure of irradiation is adequate to control pain

Conclusion

Bearing in mind that almost half of the patients died of their disease within 4 months following the single-dose treatment, it might be worth-while to emphasize the possibility of relieving an incurable patient with a malignant tumour from intolerable pain without intruding too much on the short remaining lifespan The economic, psychologic and social advantages which this implies should not be disregarded

SUMMARY

The results of single-dose irradiation of 64 patients with painful bone metastases are reported In about two thirds of the patients complete disappearance of pain was obtained

ZUSAMMENFASSUNG

Die Ergebnisse einer einzelnen Bestrahlungsdosis bei 64 Patienten mit schmerzhaften Knochenmetastasen werden berichtet Bei etwa zwei Dritteln dieser Patienten wurde ein vollständiges Verschwinden der Schmerzen erreicht

RÉSUMÉ

Présentation des résultats de l'irradiation par une dose unique de 64 malades ayant des métastases osseuses douloureuses On a obtenu une disparition complète de la douleur chez environ les deux tiers des malades

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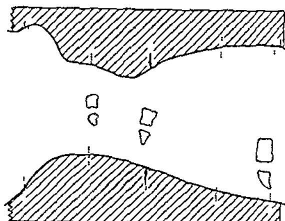


Fig 3 Anatomic section constructed from the ventral cardboard and the lateral film From this section the dorsal cardboard sheet is constructed

TAPPER & LANDBERG) Some important details in treatment set-up and the construction of the sagittal section and the individual filters for the dose planning are now described for the purpose of elucidation

For reproducible positioning of the patient two large styrofoam casts are made, one for supine and one for prone position (Figs 1 and 4) Both casts are made with the patient in one position to preserve the contour of the patient as much as possible when changing posture If also total nodal irradiation is to be given, the same casts are used for the whole sequence of treatments The arms are above the head and the neck is extended On the simulator the patient is then first placed supine in the corresponding cast and the silhouette is cut out in a sheet of cardboard, the long straight border of the cardboard sheet being horisontal (Fig 1) The levels of the cranial border of the target, the larynx, the jugulum, the lung hilum and the caudal border of the target are projected vertically to the skin of the patient as well as the borders and the centre of the beam All these levels are marked with ink and lead wires on the patient's skin and projected to the cardboard The sagittal contour of the patient both ventrally and dorsally are indicated with long tin wires

Films of known magnification are exposed while the patient swallows barium (Fig 2) The sagittal section is constructed from the ventral cardboard and the lateral films (Fig 3) From this anatomic plan in the sagittal section a new cardboard for the prone position is constructed The different levels are via the anatomic section transferred to the dorsal cardboard together with the horizontal line The patient is then placed prone in the other case (Fig 4), and the centre of the dorsal field is marked on the patient's skin with the aid of fluoroscopy to correspond to the central mark on the a p film of the ventral beam If the dorsal cardboard constructed from the supine position does not fit the contour of the patient and the centre of the beam marked under fluoroscopy, or if it deviates from the horizontal line, the cast for the prone position must be modified When all details agree between patient contour and cardboard, lateral films with known magnification and with barium in the oesophagus are exposed By comparison of the films in supine and prone position the movement of viscera is determined (SVAHN-TAPPER & LANDBERG) and a correspond-



Fig 4 The patient in the prone position It may be necessary to modify the cast to get the patient s contour to fit the cardboard sheet

ing correction can be applied to the planned absorbed dose in the oesophagus and the mediastinum

Such a correction of the absorbed dose does not apply to the spinal cord The two cardboards are used at every irradiation set up to secure exact positioning of the patient

A comparison between the sagittal section constructed from the supine position and that from the prone position agreed within one cm in the a p distances for all patients with exception for the obese females The difference was random and the sagittal section from the supine position was used

Treatment technique and dose planning Large opposed ^{60}Co beams at SSD 130 cm and equally weighted are used (Siemens Gammatron III with a moving arc collimator) The beams are blocked 22 cm from the patient to produce small penumbras The lead blocks are 5 cm thick with vertical edges In the cranio-caudal direction the same beam flattening filter is used for all patients (filter A, recalculated to be placed on the actual moving arc collimator, SVAHN-TAPPER) For the neck region individually constructed filters are added In the lateral direction no filters are used The isodose diagram in the sagittal section for the flattened field is constructed from depth dose measurements in different parts of the field using a large water phantom and supported by film exposures in a large polystyrene phantom This isodose diagram is shortened or elongated if necessary to be adapted to the size of the target in dose planning No corrections for tissue heterogeneities are made in the planning of the sagittal section The same central axis depth dose data and the same correction for the equivalent square field in irradiation time is used for all adult patients receiving a full mantle field Since *in vivo* measurements always are performed, such a generalization in treatment data is justified The field, for which the phantom measurements were performed, had a size of 38 cm × 34 cm (40 cm × 38 cm before the

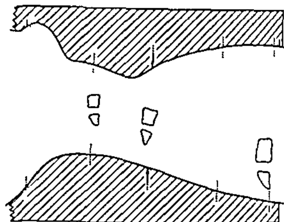


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A comparison between the sagittal section constructed from the supine position and that from the prone position agreed within one cm in the a p distances for all patients with exception for the obese females The difference was random and the sagittal section from the supine position was used

Treatment technique and dose planning Large opposed ^{60}Co beams at SSD 130 cm and equally weighted are used (Siemens Gammatron III with a moving arc collimator) The beams are blocked 22 cm from the patient to produce small penumbras The lead blocks are 5 cm thick with vertical edges In the cranio-caudal direction the same beam flattening filter is used for all patients (filter A, recalculated to be placed on the actual moving arc collimator, SVAHN-TAPPER) For the neck region individually constructed filters are added In the lateral direction no filters are used The isodose diagram in the sagittal section for the flattened field is constructed from depth dose measurements in different parts of the field using a large water phantom and supported by film exposures in a large polystyrene phantom This isodose diagram is shortened or elongated if necessary to be adapted to the size of the target in dose planning No corrections for tissue heterogeneities are made in the planning of the sagittal section The same central axis depth dose data and the same correction for the equivalent square field in irradiation time is used for all adult patients receiving a full mantle field Since in vivo measurements always are performed, such a generalization in treatment data is justified The field, for which the phantom measurements were performed, had a size of 38 cm × 34 cm (40 cm × 38 cm before the

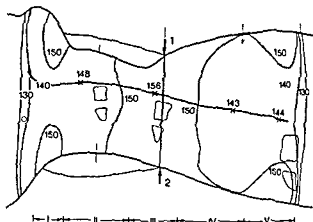


Fig 5 Dose plan for the sagittal section Fields 1 and 2, ^{60}Co, 130 cm SSD, 100% and beam flattening filter Honeycombed area = target Dashed area is recalculated to copper filter The comparison between measured and planned absorbed dose is performed in the different parts of the mantle field, here indicated I–V

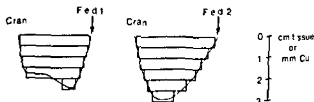


Fig 6 Individual copper filter for fields 1 and 2 for the dose plan in Fig 5

broad penumbra was blocked off) and the shaped mantle field had an equivalent square of about 25 cm × 25 cm according to calculations of the amount of scattered radiation in the centre of the field

A dose plan in the sagittal section is given in Fig 5 The higher absorbed dose at the jugulum is deliberate, since at that level a minimum exists laterally in the top of the axilla (as regards the dose distribution in lateral direction see SVAHN-TAPPER & LANDBERG) The dashed areas in the neck region represent the individual need for a compensation for the shorter anterior-posterior distance compared with the rest of the section In the dose planning these dashed areas are for practical reasons considered as tissue This fictive tissue' is then reduced in size in the plane perpendicular to the central beam to fit the filter position and the thickness is recalculated to the equivalent thickness of copper, applying the rule 1 cm tissue equals 1 mm copper (Fig 6) These individual contour compensating filters thus obtained are placed on the beam flattening filter and fixed to the collimator of the ^{60}Co machine

Measuring system and technique For the in vivo determination of absorbed dose condenser chambers of volume 0 3 cm^3, 2 cm long and 0 5 cm in diameter were used (SIEVERT 1932, SKOLDBORN 1959) All the ionisation chambers were calibrated with build up cap free in air against a substandard chamber, which had in turn been calibrated at the Standard Laboratory of the Swedish Radiation Protection Institute The coefficient of variation of a measurement is estimated to ± 3 per cent (± 2 per cent in pure phantom measurements)



Fig. 7 Slow film of the ventral beam demonstrating the position of the plastic catheter with ionisation chambers and lead indicators in the hypopharynx-oesophagus. The large white cross is the centre of the beam. Black solid line marks desirable change of the left lung shield

Since the conversion coefficient F used for the ionisation chambers is valid for a field size of 10 cm 10 cm (ICRU report 23) there is an uncertainty introduced when the chambers are used in a mantle field According to the ICRU report this error will always be less than 2 per cent The same uncertainty is introduced in the output measurement of the mantle field performed with the substandard chamber In the comparison between measured and planned absorbed dose the discussed uncertainty is estimated to one per cent Since the in vivo measurements were performed during many years systematic errors in the calibration of the ionisation chambers and in the out put measurements of the ^{60}Co machine have changed many times and can be neglected in the final results

The absorbed dose in the hypopharynx-oesophagus is routinely determined twice at the beginning of the treatment course A plastic catheter containing 16 to 20 ionisation chambers and lead indicators between every fourth chamber is introduced in the oesophagus Both the ventral and dorsal fields are irradiated and slow films exposed during the whole irradiation show the position of the catheter In Fig 7 the measuring points are marked with black crosses The centre of the beam may be indicated with a lead pellet on the patient s skin or transferred from the portal film exposed on the simulator

The influence of the lead indicators in the catheter on the measured absorbed dose is +1 per cent for the ionisation chambers placed with the air cavity nearest to the lead For the other chambers the effect of the lead can be neglected

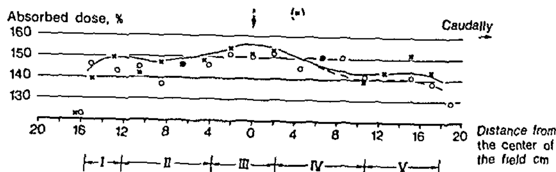


Fig 8 Absorbed dose in per cent of the peak absorbed dose along the hypopharynx oesophagus The arrow indicates the central beam The solid curve represents the absorbed dose from the dose plan (Fig 5) and the broken curve the planned dose in the oesophagus with correction for the effect of change in posture Crosses and circles indicate the measured absorbed dose at the two measuring occasions I–V indicate the division of the field for the analyses of the measurements

Correction of absorbed dose measurements Correction for the error introduced by the treatment time table is made if it exceeds 0 5 per cent This means that the measured absorbed dose is corrected for two thirds of the patients, since the error in the treatment time table normally varies with ±1 5 per cent due to correction for the ^{60}Co decay performed every 3 months If the measuring points in the hypopharynx are located just behind the trachea as observed on the slow film of the ventral beam (the two chambers between the jugulum and the larynx in Fig 7) the measured absorbed dose value is reduced by 7 per cent of the peak absorbed dose of the ventral beam according to phantom measurements (SVAHN-TAPPER)

Analyses of the measurements of absorbed dose The absorbed dose in the hypopharynx-oesophagus from the dose plan as a function of the distance from the centre of the beam appears in Fig 8 as the solid line Taking into account the movement of the oesophagus when the patient changes from supine to prone position, the planned absorbed dose should follow the broken line In the same diagram the measuring points, localized by the slow films, are marked with crosses and circles for the two catheters respectively From the diagram the difference between measured and planned absorbed dose is read for every measuring point The differences are expressed in percentage of the planned absorbed dose at the corresponding level

The mantle field is divided into five parts in the cranio-caudal direction, marked I–V in Figs 5 and 8 Part I consists of the submaxillary region, part II the neck region, part III covers a region at the level of the clavicle where the centre of the field is located, part IV includes the upper mediastinum and the hilar regions and part V the lower mediastinum

During the treatment course measurements were performed twice in the hypopharynx-oesophagus in 56 patients and three times in 4 patients Totally the absorbed dose in 1 627 points are analysed for the 60 patients, 40 males and 20 females The number of measurements in different parts of the mantle field are given in Table

Table 1

Number of patients and measurements analysed in different parts of the mantle field The length in cranio-caudal direction of the different parts I V

	Part I	Part II	Part III	Part IV	Part V
Number of patients	56	60	60	60	59
Total number of measurements	195	376	312	352	392
Number of measurements patient					
Mean	3.5	6 3	5 2	5 9	6 6
SD	1 2	2 2	1 1	1 2	2 4
Range	2-6	2 10	2 8	2 10	2 14
Length of the different parts (cm)					
Mean	4	7 5	6	7	8
Range	2 5	5 11	6-6	5 9	6 14

1 The figures after the means are the standard deviations (SD) and ranges The lengths of the different parts (I V) appear in the same table

Conditions for acceptance of the measured absorbed dose values All the analysed catheters with ionisation chambers have moved less than ± 0.7 cm during the irradiation of the two fields Measurements in the penumbra regions are excluded in the analyses If a measured absorbed dose value deviates more than 8 per cent from the adjacent 3 to 4 chamber values it is excluded since occasionally an increased or complete discharge of the chamber may occur due to mechanical shock or high humidity (SKÖLDBORN) In Fig 8 the cross in the parenthesis 4 cm caudally of the field centre is an example of such a failure On the average one or two absorbed dose values per patient are omitted due to an increased discharge and about three values per patient had to be omitted due to complete discharge of the ionisation chamber Measurements from obviously wrong irradiations are also excluded, for example if the filters were erroneously orientated in cranio-caudal direction or if the treatment time had been incorrect for one of the fields

Definition of the patient s size The mean value of the three anterior-posterior (a p) distances at the level of the larynx, at the level of the jugulum and at the level of the lung hilum is chosen as a measure of the patient's size These distances are well defined from the films (Fig 2) The 10 patients with the smallest mean in a p distances are defined as thin patients and the 10 patients with the largest means of the a p distances are called stout patients The others are called normal Table 2 gives the mean and the range in a p distance for the whole group of patients, for the 10 thin patients and for the 50 stout+normal patients In the same table the patients' weights are presented as well as the lengths of the fields in cranio-caudal direction The number of measurements in the different patient groups also appears

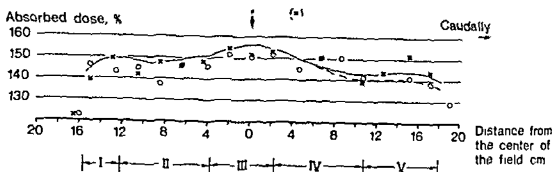


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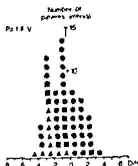


Fig 9 Distribution of the difference between the measured and planned absorbed dose as per cent of the planned absorbed dose (Diff) for part II-V of the mantle field Total number of patients – 60 ▲ – thin, ● – normal, and ■ – stout patient.

Results and Discussion

The histograms in Figs 9 and 10 a–e show the distribution of the difference between the measured and the planned absorbed dose as per cent of the planned absorbed dose both for the whole mantle field (Fig 9) and for the different parts of the mantle field indicated in Figs 5 and 8 The mean, the standard error of the mean (SEOM) and the standard deviation (SD) of the histograms are listed in Table 3 In the histogram of the whole mantle the submaxillary region is excluded, because the dose distribution in that part of the mantle is closely related to the degree of fixation of the chin Since such a small part of the field near the border is not representative for the scattering conditions of the remainder of the mantle field, it can be excluded

The means of the difference between measured and planned absorbed dose at the various locations are for all the 60 patients within $-(0\,4 \pm 3\,2)$ per cent and $-(1\,3 \pm 2\,9)$ per cent The difference is only statistically significant at the clavicle ($p < 0\,025$) and in the caudal part of the mediastinum ($p < 0\,001$) The means for the thin patients are for the different parts II, III, IV and V between $(1\,7 \pm 1\,9)$ per cent and $(3\,1 \pm 2\,4)$ per cent and the measured and planned absorbed dose differs significantly in all anatomic sites with exception for the submaxillary region (p $0\,014$, p $0\,004$, p $0\,002$ and p $0\,003$ from the neck to the lower mediastinum) There is also a significant difference of the means for the thin patients compared with the 50 normal – stout patients ($p < 0\,025$, $p < 0\,050$, $p < 0\,001$ and $p < 0\,025$ from the neck to the caudal mediastinum) For the 50 normal + stout patients the variation in the means are from $+(0\,4 \pm 3\,4)$ per cent to $(0\,9 \pm 2\,9)$ per cent where the deviation between measurements and dose planning is significant only in the lower mediastinum (p $0\,025$)

An attempt to classify the small patients from the size of the unblocked mantle field failed and so did an attempt to group the patients with respect to the product of the a p distances and the unblocked field sizes The unblocked field size was used since an estimate of the blocked field size afterwards appeared to be too uncertain Thus the thickness of the patient seems to be the best measure of the treatment volume, an opinion that agrees with the assumption by PAGE et coll (1970) in

Table 2

A p distances, weights, field lengths and number of measurements for all the 60 patients, for the 10 thin patients and the 50 normal + stout patients

	All 60 patients	10 thin patients	50 normal + stout patients
A p distance (cm)			
Mean	*16 5*	*13 9*	*17 0*
Range	13 2–20 7	13 2–14 7	14 8–20 7
Weight (kg)			
Mean	*65*	*51*	*68*
Range	*38–101*	*38–61*	*54–101*
Field length (cm)			
Mean	*38 0*	*37 6*	*38 1*
Range	31 5–43	34–41	31 5–43
Number of measurements (submaxillary region excluded)	1 432	208	1 224

Table 3

Difference between measured and planned absorbed dose as per cent of planned absorbed dose in the anatomic sites I–V for all the 60 patients, for the 10 thin patients and for the 50 normal + stout patients

	Part II–V	Part I	Part II	Part III	Part IV	Part V
All 60 patients						
Mean	−0 6	+0 4	0 2	−0 7	−0 3	−1 3
SEOM	0 3	0 5	0 4	0 4	0 3	0 4
SD	1 8	3 2	2 5	2 5	2 4	2 9
10 thin patients						
Mean	2 4	−0 0	1 7	2 0	−3 0	−3 1
SEOM	0 4	0 8	0 6	0 6	0 5	0 8
SD	1 1	2 1	1 9	1 8	1 6	2 4
50 normal + stout patients						
Mean	0 2	0 4	+0 1	0 5	+0 2	−0 9
SEOM	0 3	0 5	0 4	0 4	0 3	0 5
SD	1 7	3 4	2 5	2 5	2 2	2 9

The statistical analysis of the results The comparison of the measured and planned absorbed dose values were statistically analysed both for the whole patient group and for the thin patients compared with the normal + stout patients In the significance test of the difference between measured and planned absorbed dose the Wilcoxon's sign test was used In the comparison of the thin patients and the normal + stout patients the t-test was used The rounding in standard error of the mean (*SEOM*) and standard deviation (SD) was always performed upwards

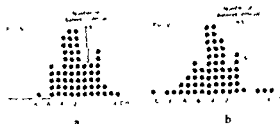


Fig 11 Distribution of the difference between measured and planned absorbed dose as per cent of the planned absorbed dose (Diff) for part IV and V without correction of the planned dose for movement of the oesophagus when the patient changes posture ● – patient

(Table I) and partly on the lack of a perfect fixation of the chin Furthermore it may be an effect of the simple method of shortening and elongation of the isodose chart to fit the length of the target The same effect may have an influence on part V (the lower mediastinum)

Part II In the neck region (Fig 10 b) an additional uncertainty in the analyses of the measurements occurs due to the correction for the air cavity in the trachea Such a correction was justified in 22 of the 60 patients, sometimes only in the measurements at one of the fractions depending on the position of the catheter related to the trachea No correction for this air cavity was performed in the dose plan, since enlarged lymphnodes are seldom found in the midplan of the neck in Hodgkin's disease Without correction the dose plan will simulate the dose distribution in the medial parts of the lymph nodes of the neck Furthermore the measurements in this region is a control of the method of constructing filters for lacking tissue The equivalence of one cm tissue and one mm copper seems to be a good approximation A filter like this is only correct at one depth (LEUNG et coll, SÖRENSEN & SELL 1972), but since the hypopharynx is located almost at the centre of the lymph nodes from anterior posterior view and the irradiations were given both with a p and p a beams, the error due to different filtering effect with depth may be neglected The effect of the limited thickness of scattering media beneath and adjacent to the neck, which by CUNDIFF et coll was estimated to be between 2 and 0 per cent, seems to be mutually compensatoried by the filter

Part III In relation to the anatomy of the patient the centre of the field was not fixed from one patient to another, but it always fell in the clavicular region That means that the correction in SSD is smallest in this part of the field The 3 patients in Fig 10 c with a larger difference than 5 *per cent* (~2 SD) between measured and planned absorbed dose were all obese females with large breasts In these patients it is difficult to define and reproduce the a p distance correctly

Part IV In the upper mediastinum the largest differences between the thin patients and the other patients were found (*Fig 10 d* and Table 3) The variance of the distribution was smallest at this anatomic site The analyses of the measurements was

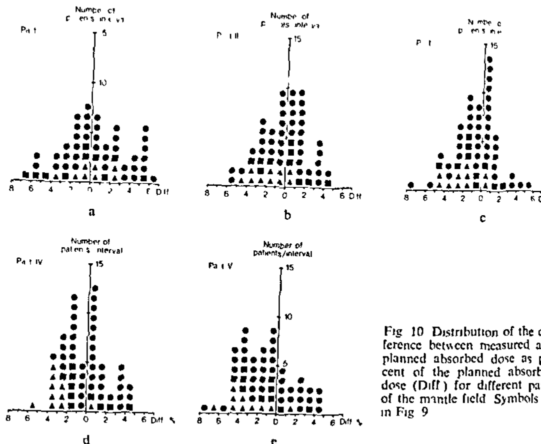


Fig 10 Distribution of the difference between measured and planned absorbed dose as per cent of the planned absorbed dose (Diff) for different parts of the mantle field Symbols as in Fig 9

their dose calculation for the mantle field 'The actual dose received is more dependant on the thickness and SSD at any particular site than on field shape' Measurements of absorbed dose in a water phantom in the field centre at a depth of 5 cm and 15 cm showed a difference of ± 1 per cent and ± 2 per cent, respectively, if a mantle field for a stout and a thin patient was compared with a field for a normal patient (SVAHN-TAPPER) Thus the measurements in the thin patients analysed show the same tendency as the corresponding phantom measurements

In the comparison of the 10 stout patients and the 40 normal patients no significant difference in measured and planned absorbed dose was found Thus the stout patients may be considered as normal from a dosimetric point of view According to the water phantom measurements it is expected that the measured absorbed doses compared with the planned doses should be somewhat higher than for the normal patients Some other factors may have masked this effect, for instance the thicker filter in the neck region and a different blocking technique Since these patients often need a large field, the collimator has to be turned 45° to use the diagonal of the field in the cranio-caudal direction

Part I The greatest variance in the distribution was found in the submaxillary region (Fig 10 a) This depends partly on a smaller number of measurements per patient

Table 4

Absorbed dose, in per cent of peak absorbed dose, in points A to E according to measurements and to calculations from the diagram of SVAHN-TAPPER & LANDBERG (1971)

Points	Measured absorbed dose	Calculated absorbed dose
A	145	—
B	163	162
C	157	158
D	147	—
E	144	—

give a difference between real absorbed dose and treatment planning of as much as 10 per cent as is evident from the histogram

Frequency of errors Errors in irradiation time were found in less than 2 per cent of the fractions Erroneous filter orientation occurred in less than 1 5 per cent of the fractions Before performing the final comparison between measured and planned absorbed dose the outlines of the sagittal sections were checked against the lateral films It was found that in 8 per cent of the sections constructed in the clinical routine, an error in a p distance in some part of the section occurred that would have given an error in target absorbed dose of more than 5 per cent in the absence of in vivo dose control Usually the wrong part of the section was found in the submaxillary and neck regions In vivo measurements may eliminate errors due to wrong sections entirely and errors from wrong irradiation set-up partly, since the detection of errors makes the staff aware of the pitfalls

Lung hilum measurement The measurements in the hypopharynx-oesophagus caused no side effects in the patients, not even when the catheter passed into the trachea This happened in one patient and was detected from the films exposed during the irradiation Fig 12 demonstrates the position of the ionisation chambers in the left bronchus The measured absorbed dose values in points B–E are given in Table 4 The absorbed dose in the centre of the mediastinum was measured in a previous fraction with the catheter in the oesophagus giving in point A 145 per cent of the peak absorbed dose The patient's a p distance at the corresponding level was 19 cm If the factors from the curves for lung correction presented in Fig 13 of the report by SVAHN-TAPPER & LANDBERG are applied to the absorbed dose in point A, the corresponding corrected figures are 1 12 × 145 per cent = 162 per cent for point B (curve B) and 1 09 × 145 per cent = 158 per cent for point C (curve C, to be used behind the heart) The measured absorbed doses were 163 and 157 per cent respectively, for point B and C The measurements do not contradict the calculation method for absorbed dose distribution in the lung hilum



Fig 12 Slow film exposed during treatment catheter with ionisation chambers in the left bronchus The measured absorbed dose values in points A to E are given in Table 4

most straightforward here since in this part of the field there was no individual filter no correction of the measurements for air cavity in the trachea and no shortening or elongation of the field with respect to the target

Part V The field length will influence the absorbed dose in the caudal part of the mediastinum more than in the central part of the field In the present material the field length in cranio caudal direction varied between 31 5 cm and 43 cm Calculations performed from the scatter functions have shown that a shortening or elongation of the field caudally by +4 cm alters the absorbed dose in the centre of the lower mediastinum with +(1–2) per cent (SVAHN TAPPER) Furthermore the patient s breathing affects the a p distance most in this part of the field The broadening of the histogram (Fig 10 e) may partly be explained by these facts

For the group normal + stout patients significant differences between measured and planned absorbed dose were only found in this part of the mantle (p 0 025)

The movement of viscera Fig 11 a and b show a comparison between measured and planned absorbed dose for the cranial and caudal parts of the mediastinum respectively disregarding the movements of the oesophagus when the patient changes from supine to prone position The histograms should be compared with Fig 10 d and e respectively Such a movement appeared in two thirds of the patients In 12 of the 60 patients this movement alone would have given an error of more than 4 per cent in target absorbed dose if not corrected for The combination of a neglected oesophagus movement and a low absorbed dose for other reasons may

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Conclusion

The mantle treatment is from many points of view complex The large and irregular field, the varying shape of the target due to the patient or to bulky disease, the tissue heterogeneities within the field and in its blocked parts, the varying degree of back and side scattering material and the large variation in patient surface contour within the field are all parameters that influence the distribution of absorbed dose Thus, it is satisfying to find that for the technique used the mean difference between in vivo measured and planned absorbed dose estimated for different anatomic sites along the hypopharynx-oesophagus is within +0 4 and −1 3 per cent with a standard error of the mean of 0 4 per cent for 60 patients In the regions from the neck to the lower part of the mediastinum at most 3 patients have a larger difference than 5 per cent between measured and planned absorbed dose The obese females belong to these patients With a better fixation of the chin the agreement with measured and planned absorbed dose in the submaxillary region ought to be as good as for the rest of the mantle field

Since the dosimetry in the lateral parts of the mantle field is based on the same system with dose planning and in vivo control of the absorbed dose (SVAHN-TAPPER, SVAHN-TAPPER & LANDBERG) there is no reason to doubt the correctness of the dose distribution in the entire mantle field

In summary it may be said that in mantle treatment with ^{60}Co

a) it is possible to use isodose charts with the 'two third' correction for oblique incidence,

b) it is possible to use the same depth dose values for all patients (if a correction is performed according to point c),

c) there is no need for a correction in machine out-put due to difference in scattered radiation with exception for very thin patients, where the correction is less than +2 5 per cent of the peak absorbed dose,

d) it is possible to use the same beam flattening filter in cranio-caudal direction for all patients,

e) the distribution of absorbed dose in the target is illustrated in a good way by planning of a sagittal section,

f) no corrections for tissue heterogeneities is needed except in the hilar regions, and

g) the movements of viscera when the patient is irradiated in two positions must be regarded

All this is valid only if the patient is correctly and reproducibly fixed during the treatment and if the patient's external contour is preserved when the posture is changed The technique described has a good reproducibility when used at other centra The accessories are cheap and computers are not required for the planning of the absorbed dose distribution

Acknowledgement

This investigation was supported by grants from the Swedish Cancer Society

SUMMARY

In vivo dose measurements were performed in the hypopharynx-oesophagus for 60 adult patients receiving mantle treatment with ⁶⁰Co The measurements of absorbed dose in more than 1 600 points were analysed and compared with dose plans for the same patients For the technique used the mean difference between in vivo measured and planned absorbed dose is within +0 4 and 1 3 per cent with a standard error of the mean of 0 4 per cent

ZUSAMMENFASSUNG

In vivo Dosismessungen wurden im Hypopharynx-Oesophagus bei 60 erwachsenen Patienten, die mit der Manteltechnik mit ⁶⁰Co behandelt wurden, vorgenommen Die Messungen der absorbierten Dosis in mehr als 1 600 Punkten wurden analysiert und mit den Dosisplanen desselben Patienten verglichen Bei der verwendeten Technik betrug die mittlere Differenz zwischen der in vivo gemessenen und der geplanten absorbierten Dosis zwischen +0 4 und −1,3 Prozent mit einem mittleren Standardfehler von 0,4 Prozent

RÉSUMÉ

Les auteurs ont effectué in vivo des mesures de doses dans l hypo-pharynx et l oesophage de 60 malades adultes subissant un traitement en mantelet par ⁶⁰Co Les mesures de la dose absorbée en plus de 1 600 points ont été analysées et comparées avec les plans de dose pour les memes malades Avec la technique utilisee, la différence moyenne entre les mesures in vivo et les doses absorbées prévues par le plan de traitement est comprise entre +0,4 et −1 3 pour cent, avec une erreur standard de la moyenne de 0,4 pour cent

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[illegible]
ICR [illegible] 7
b [illegible] gle

Conclusion

The mantle treatment is from many points of view complex The large and irregular field, the varying shape of the target due to the patient or to bulky disease, the tissue heterogeneities within the field and in its blocked parts, the varying degree of back and side scattering material and the large variation in patient surface contour within the field are all parameters that influence the distribution of absorbed dose Thus, it is satisfying to find that for the technique used the mean difference between in vivo measured and planned absorbed dose estimated for different anatomic sites along the hypopharynx-oesophagus is within +0 4 and −1 3 per cent with a standard error of the mean of 0 4 per cent for 60 patients In the regions from the neck to the lower part of the mediastinum at most 3 patients have a larger difference than 5 per cent between measured and planned absorbed dose The obese females belong to these patients With a better fixation of the chin the agreement with measured and planned absorbed dose in the submaxillary region ought to be as good as for the rest of the mantle field

Since the dosimetry in the lateral parts of the mantle field is based on the same system with dose planning and in vivo control of the absorbed dose (SVAHN-TAPPER, SVAHN-TAPPER & LANDBERG) there is no reason to doubt the correctness of the dose distribution in the entire mantle field

In summary it may be said that in mantle treatment with ^{60}Co

a) it is possible to use isodose charts with the 'two third' correction for oblique incidence,

b) it is possible to use the same depth dose values for all patients (if a correction is performed according to point c),

c) there is no need for a correction in machine out-put due to difference in scattered radiation with exception for very thin patients, where the correction is less than +2 5 per cent of the peak absorbed dose,

d) it is possible to use the same beam flattening filter in cranio-caudal direction for all patients,

e) the distribution of absorbed dose in the target is illustrated in a good way by planning of a sagittal section,

f) no corrections for tissue heterogeneities is needed except in the hilar regions, and

g) the movements of viscera when the patient is irradiated in two positions must be regarded

All this is valid only if the patient is correctly and reproducibly fixed during the treatment and if the patient's external contour is preserved when the posture is changed The technique described has a good reproducibility when used at other centra The accessories are cheap and computers are not required for the planning of the absorbed dose distribution

FROM THE DEPARTMENT OF PHYSICS (DIRECTOR A SIIVOLA) UNIVERSITY OF HELSINKI AND THE DEPARTMENT OF RADIATION THERAPY (DIRECTOR PROFESSOR L. R HOLSTI) UNIVERSITY CENTRAL HOSPITAL, HELSINKI FINLAND

EXPERIMENTS ON RADIATION-INDUCED TUMOUR

Theoretical view-points

K PAASIKALLIO E SPRING and M SALMO

Although numerous investigations have been concerned with radiation carcinogenesis means are still lacking for derivation from tumour incidence experiments of the physical parameters that describe the radiation sensitivity of the irradiated tissue If a method could be found to calculate these parameters by application of current knowledge of tumour induction and recurrences as a function of the radiation dose it would be possible in the future to calculate the most dangerous tumour inducing dose before a patient is irradiated Consequently the risk of radiation induced cancer and recurrences would be reduced

At present however most of the experiments relating to induced tumour incidences have been made with single doses given to mice and rats of different strains More over

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At present, however, most of the experiments relating to induced tumour incidences have been made with single doses given to mice and rats of different strains. Moreover, the radiation qualities used have differed a great deal, and the irradiated fields range from total body to small fields. A comparison of different experiments is thus rendered difficult. Furthermore, many sources of error are introduced by the different times for autopsy. The animal may have died before the induced tumour has had time to develop into a clinically detectable form; in some cases one or more of the multiple tumours induced may have been disregarded. When results from the literature have been compared, the doses used in the original report have been maintained (R or rad). Dose in the present report always means absorbed dose.

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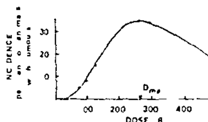


Fig. 1

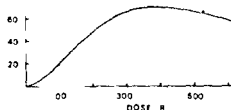


Fig 2

Fig 1 Dose response relations for the induction of myeloid leukaemia in male mice by whole body irradiation experimental results – (UPTON 1961) curve calculated by the authors

Fig 2 Dose response relations for the induction of mammary tumours in total body irradiated female rats, experimental results (BOND et coll 1960) curve calculated by the authors

An interesting method for the calculation of values of D_0 and n for an induced tumour cell has been given by GRAY who derived the model by employing the experimental values given by UPTON et coll for the induction of myeloid leukaemia Since most survival curves have rather flat shoulders i e few cells are killed at low doses he made the assumption that the very beginning of the experimental tumour incidence curve might be used for definition of the dose dependence of the induction process Thus the extrapolation of this part of the curve to higher doses would indicate the tumour induction relationship to the radiation dose if the assumption was made that no cells were killed By dividing the observed incidence values by the values of the extrapolated curve he obtained the probability that radiation induced tumour cells would survive GRAY thus represented the tumour incidence by the product of a survival function $S = 1 - (1 - \exp(-D/D_0))^n$ and a power law of induction KD^N with K and N being constant values for tumour incidence curve and obtainable from the fitting of the model to the experimental curve The maximum occurred with zero as the differential coefficient of the product S KD^N In the simplest case when n = 1 the product would become $KD^N \exp(-D/D_0)$ and the maximum incidence occur when

$$\frac{d}{dD}(KD^N \exp(-D/D_0)) = 0 \quad \text{i e} \quad D_{max} = ND_0$$

In the general case when n is not equal to 1 accurate evaluation of the equation is impossible If however the approximation $1 - (1 - \exp(-D/D_0))^n = 1 - (1 - n \exp(-D/D_0)) = n \exp(-D/D_0)$ is made the result obtained would be the same as before, with the maximum still occurring when $D_{max} = ND_0$

On comparison of these two models they are seen to represent two quite different approaches to the problem The first gives the D_0 and n values for the irradiated normal tissue and the second the corresponding values for the radiation induced tumour cells which appear during the irradiation of the normal tissue It is interesting

An increase in the number of thymic leucaemias has been shown in experiments with ^{57}C mice (KAPLAN & BROWN 1952). When similar *experiments were performed* in the myeloid leucaemia of RF mice, no increase was observed (UPTON et coll. 1958). There is a general agreement that equal doses give less marked effects with protracted irradiation (FABER 1969).

SPRING et coll. (1972) have analysed recurrences in irradiation of laryngeal carcinoma in a series of 31 patients, 12 of whom developed recurrences. It was clearly demonstrated that if a low probability of recurrence was to be attained, the treated volume should exceed 260 cm^3, and that *the maximum cell survival fraction within* this volume should exceed 0.3×10^{-9}. The survival values were calculated by means of single-hit, multi-target model $S = 1-(1-\exp(-D/D_0))^n$ with $n = 2$ and $D_0 = 160$ rad.

Previously SPRING & PAASIKALLIO (1973) proposed an equation for description of the induction of kidney tumours of rats. An attempt has now been made to find out if this also could be used for other radiation-induced tumour incidence curves.

GRAY (1965) has developed a model for the induction of tumours, which describes the survival of a radiation-induced tumour cell.

These two models have been employed for analysis of the results of different experiments concerned with radiation induced tumour incidences. The models are furthermore compared, and the results of the calculations are discussed.

Models

The main purpose was to investigate radiation induced tumour incidence curves presented in the literature, and to test the validity of the following induction equation of SPRING & PAASIKALLIO

$$I = gn(1-\exp(-D/D_0))^{n-1}\exp(-D/D_0) \quad (1)$$

D is the radiation dose (single dose), and D_0 the dose required to reduce the number of surviving cells from any value N to 0.37 N. This is obtained from the slope of the straight part of the survival curve, n is the extrapolation number, and g is a constant with different values for different kinds of induced tumours. The dose which gives maximum induction incidence, i.e. the most critical dose for tumour induction, is obtained from the following equations

$$\frac{dI}{dD} = 0 \quad \text{which gives} \quad D_{max} = D_0 \ln n \quad (2)$$

D_{max} is directly obtainable from each tumour-incidence curve (Fig. 1). When D_{max} is known, different D_0, n pairs may be calculated from eq. *(2). These values of D_0* and n are substituted into eq. (1), and the best fit is found by use of the method of least squares. It is assumed that the pair of D_0 and n which gives the best fit represents the radiation sensitivity of the irradiated tissue, in the same way as it is known and used in radiation therapy.

Table (*cont.*)

D_{max}	n	D_o	n	D_o	Field size
	Own model		Gray's model		
270 R	5	170 R	3*	120 R*	Total body
400 R	3	360 R	3**	190 R**	Total body
4 700 rad	—	—	1.9	2 290 rad	Partial body field of 8.6 cm²
4 200 rad	4	3 030 rad	1.2	2 440 rad	
2 000 rad	15	740 rad	5	630 rad	3 cm 8 cm
1 700 rad	15	630 rad	—	—	2 inch 4 inch (5.08 cm 10.16 cm)
888 R	3	810 R	5	300 R	Anterior half of the animal
1 500 R	16	540 R	—	—	Lung area
1 710 rad	9	870 rad	—	—	One kidney

that of the fitted curve. The parameter values obtained by the fitting are within the limits of the cell survival parameter values that are usually obtained.

The fitting of the mammary tumour curve (Fig. 2) by eq. (1) is not exact. However, the parameter values obtained seemed quite reasonable (Table). A source of error in this tumour induction experiment might be that the irradiated rats were killed 10.5 to 11 months after the irradiation, this is the time period during which essentially no neoplasms of other origin than the breast occurred in the exposed rats, or in the breast tissue of those not subjected to irradiation.

The parameters calculated with GRAY's model do not exhibit any appreciable differences from those obtained by eq. (1) (Table). The values for the induced leukaemia were calculated by GRAY, and the corresponding values for mammary tumours are the results of the present calculations.

Partial body irradiation. Induced skin tumours

The second group of induced tumours comprised skin irradiations with β-particles of different energies.

The first experiments of this type were carried out by HULSE (1967) and HULSE et coll. (1968). The irradiation source was an open-ended cylindrical foil, 1.1 cm in

Table

A compilation of the experimental values used and the theoretical results calculated

Authors	Irradiated animals *	Irradiation	Induced tumour
UPTON 1961	RF male mice	Rtg-rays	Myeloid leukemia
BOND et coll 1960	*Female Sprague-* Dawley rats	*250 kVp rtg rays*	*Mammary tumours*
HULSE 1967	CBA/H mice	β-radiation from ^{204}Tl	Dermal tumours
HULSE et coll 1968	CBA/H mice	β-radiation *from* ^{204}*Tl*	Epidermal tumours
ALBERT et coll 1967 a	Male albino rats, CD	β-radiation (van de Graaff)	Skin tumours
ALBERT et coll 1967 b	Male Sprague-Dawley rats	β-*radiation* (van de Graaff)	*Skin tumours*
SHELLABARGER & SCHMIDT 1967	Female Sprague-Dawley rats	250 kVp rtg-rays	Mammary tumours
YUHAS & WALKER 1973	Male RFM mice	300 kVp rtg-rays	Lung tumours
MALDAGUE 1969	Male Wistard rats	250 kVp rtg-rays	Kidney tumours

* Calculated by GRAY (1965)

** The present calculations with GRAY's model

to compare these parameter values with each other, to determine whether major differences exist between them

Even the equations for D_{max} values are somewhat different In eq (2), ln n has been replaced by the exponent N from the power law of induction

Results

The different tumour-incidence curves are illustrated in Figs 1 to 8 Each figure indicates the best fit obtained by eq (1) when fitted to the experimental curves The spontaneous tumour incidences have been subtracted from the curves

The parameter values which gave the best fit, and the corresponding values calculated by the method derived by GRAY appear in the Table

Total body radiation Induced leukaemia and mammary neoplasia

Figs 1 and 2 illustrate two whole-body irradiations The induced tumours are myeloid leukaemia in Fig 1 (UPTON et coll), and mammary tumour in Fig 2 (BOND et coll 1960) Eq (1) seems to follow the leukaemia incidence quite well, although the slope of the last part of the induced leukaemia incidence is somewhat steeper than

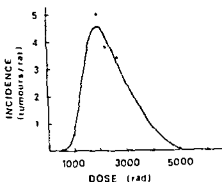


Fig 4

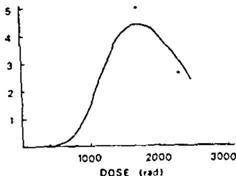


Fig 5

Fig. 4 Dose response relations for the induction of skin tumours by electron radiation, experimental results (ALBERT et coll 1967 a) curve calculated by the authors

Fig 5 Dose response relations for the induction of skin tumours by grid and sieve electron irradiations of rats experimental results (ALBERT et coll 1967 b) curve calculated by the authors

The fitting of eq (1) to the incidence curve is illustrated in Fig 4 Again, it is discernible that the fitting is rather inexact at large doses, although the curve quite well follows the experimental results on both sides of D_{max} The parameter values, moreover, are unusually large (Table), particularly the n value of 15

In this case, the threshold dose of 500 rad made it difficult to employ GRAY's model Extrapolation of the first part of the curve was effected by means of the power law, in which the threshold dose had been subtracted from the actual dose, i e $K(D - D_{tresh})^N$ instead of KD^N As a consequence of this approximation, the model is incapable of describing the zero incidence when the radiation dose is less than the threshold dose

On comparison of the parameters derived by eq (1) with those calculated with GRAY s model, major divergences are apparent between the n values (Table)

The second work of ALBERT et coll , concerned with induced skin tumours, describes the tumour yield after single exposures of β radiation, using uniform grid or sieve radiation at several dose levels The results of the uniform radiation are the only ones used in the present calculations

Induced tumours have not been divided into dermal and epidermal and the skin tumour incidence has been represented as the function of the surface dose (Fig 5) The fitting of eq (1) gives results very similar to those obtained in the previous calculations (Table)

Partial body irradiation Induced mammary, pulmonary and renal tumours

The experiments with induction of mammary tumours by total body irradiation were continued with partial body irradiation (SHELLABARGER & SCHMIDT 1967 In this experiment, the rats were followed during their entire life span Fig 6 represents

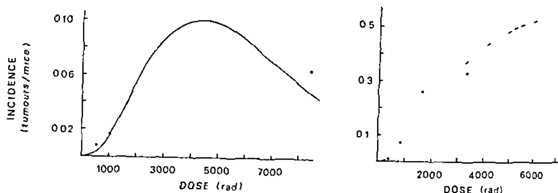


Fig 3 Dose response relations for the induction of epidermal (left), and dermal (right) tumours in partial body irradiated mice, experimental results = o (HULSE 1967) curve calculated by the authors

length, and 2 5 cm in diameter The irradiation area becomes a zone of skin 8 6 cm^2 in area Some of the mice were irradiated over one zone of skin, and other over two zones separated by an unirradiated strip For this reason, the tumour incidence has been expressed as tumours per zone This could be done, since the number of tumours after the irradiation of the two zones was not significantly different from twice the number of single zone irradiations (HULSE)

The induced tumours were divided into epidermal and dermal tumours, with the incidences being expressed as a function of the doses received by the epidermis or the dermis, and not as a function of the nominal air doses (Fig 3)

The fitted curve again remains somewhat below the experimental points Eq (1) is not fitted to the data of the dermal tumours, as the D_{max} value was unobtainable from the experimental points

HULSE et coll have calculated parameters D_0 and n by the application of GRAY's method for both these tumour frequencies (Table)

On mutual comparison the parameters calculated from eq (1) are higher than those obtained by GRAY's model Both models give D_0 values that are about ten times as high as the D_0 values usually given as representing normal mammalian cells

ALBERT et coll (1967 a, b) found that formation of radiation-induced skin tumours was highly dependent upon the penetration depth of electrons for a wide range of surface doses They used electrons with maximum ranges in the skin of 0 36 mm, 0 75 mm, and 1 40 mm It proved that if the tumour incidence was expressed as a function of the dose at a depth in the skin of 0 27 mm, the dose response curves for the three electron penetrations became congruent (Fig 4) Dermal and epidermal tumours were represented together as skin tumours Most probably, the dose at 0 27 mm depth in the skin is the dermal dose Thus, a comparison of this incidence curve with those of HULSE should be made after summation of the data of dermal and epidermal tumour-incidence, and presenting this as a function of the dermal dose However, the difficulties that arise are the same as those presented in Fig 3, it is impracticable to arrive at any reliable value for D_{max}

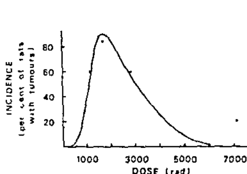


Fig 8

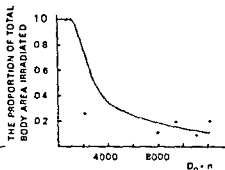


Fig. 9

Fig 8 Dose response relations for the induction of kidney tumours in mice and rats by partial body irradiations experimental results ○ (MALDAGUE 1969) curve calculated by the authors
Fig 9 The induction of tumours as a function of irradiated body area in percentage and the product of parameters D_0 and n

kidney tumours (Fig 8) The parameters that it gives for D_0 and n are also rather high in this case (Table)

Extrapolation of the first part of the curve of induced kidney tumours does not provide a resonable survival curve, as a consequence of the rapid increase in incidence between doses of 855 and 1140 rad

Discussion

In all investigations concerned with radiation carcinogenesis, a point is reached at which an increase in the dose no longer produces an increase in the tumour yield When the dose is further increased, a reduction in the tumour incidence becomes apparent

The two models (GRAY SPRING & PAASIKALLIO), which describe tumour induction provide somewhat different values for parameters D_0 and n The values calculated by GRAY s model are always less than those derived by eq (1) It was assumed that GRAY s parameters represented the survival of the induced tumour cells, and the others the survival of the irradiated normal cells

As the parameters obtained for the normal cells have such high values, it seems more probable that they represent the induction of the tumour rather than the survival of the irradiated tissue This is also observable from eq (2) $D_{max} = D_0 \ln n$, which gives D_{max} 0 rad when n is zero, i e no tumours should be induced when the cells are killed with a single hit process Moreover, if D_0 and n have high values, the maximum incidence of induced tumours is attained with large doses, if the parameters have small values the induced tumours appear with small doses

As could be observed with mammary tumours, the induction of tumours seems to be a function of the irradiated area of the animal (or the irradiated volume) Fig 9

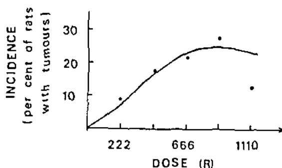


Fig 6

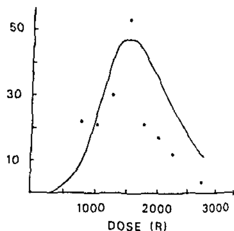


Fig 7

Fig 6 Dose response relations for the induction of mammary tumours in partial body irradiated rats experimental results = o (SHELLABARGER & SCHMIDT 1967) curve calculated by the authors

Fig 7 Dose response relations for the induction of lung tumours in mice by partial body radiations experimental results = o (YUHAS & WALKER 1973) curve calculated by the authors

the experimental incidence, and calculations made by eq (1) The corresponding parameters are listed in the Table The authors calculated D_0 and n values with GRAY's model (Table) Once again major divergences are evident between the two D_0 values, with that derived for the normal tissue being considerably higher

On comparison of the incidence curves of the induced mammary tumours (Figs 2, 6) with each other, it becomes evident that the dose for maximum tumour induction changes from 360 rad to 810 rad on a change in the irradiation field from total body radiation to irradiation of the anterior half of the animal This may explain why D_0 values calculated for partial body irradiation exceed those for total body irradiation, although in both experiments the irradiated animals and the radiation are the same *It thus becomes obvious that tumour induction is not only a function of the irradiated animal and the quality of the irradiation*

The two remaining cases of partial body irradiation were effected with localised exposures In the first experiment, lung tumours were induced by chest exposures (YUHAS & WALKER 1973), and the second was concerned with the induction of kidney tumours (MALDAGUE 1969)

The chest exposed mice were killed at about 14 months of age (11 months after the irradiation) for analysis Lung tumours detected were as small as 0 1 mm in diameter

In this case, when eq (1) is fitted to the incidence curve, a rather poor fit is obtained, (Fig 7) In fact the equation does not seem to define the tumour incidence Neither was it possible to represent this incidence curve with GRAY's model, in view of the vagueness of the dose response of low doses

Eq (1) has been derived by means of the experimental values for the induction of

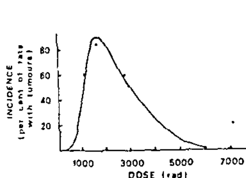


Fig 8

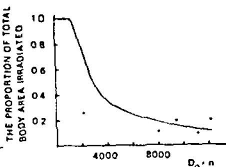


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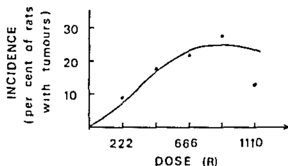


Fig 6

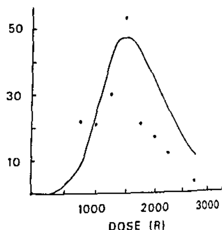


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Fig 7 Dose response relations for the induction of lung tumours in mice by partial body radiations experimental results = ○ (YUHAS & WALKER 1973) curve calculated by the authors

the experimental incidence, and calculations made by eq (1) The corresponding parameters are listed in the Table The authors calculated D_0 and n values with GRAY's model (Table) Once again major divergences are evident between the two D_0 values, with that derived for the normal tissue being considerably higher

On comparison of the incidence curves of the induced mammary tumours (Figs 2, 6) with each other, it becomes evident that the dose for maximum tumour induction changes from 360 rad to 810 rad on a change in the irradiation field from total body radiation to irradiation of the anterior half of the animal This may explain why D_0 values calculated for partial body irradiation exceed those for total body irradiation, although in both experiments the irradiated animals and the radiation are the same It thus becomes obvious that tumour induction is not only a function of the irradiated animal and the quality of the irradiation

The two remaining cases of partial body irradiation were effected with localised exposures In the first experiment, lung tumours were induced by chest exposures (YUHAS & WALKER 1973), and the second was concerned with the induction of kidney tumours (MALDAGUE 1969)

The chest-exposed mice were killed at about 14 months of age (11 months after the irradiation) for analysis Lung tumours detected were as small as 0 1 mm in diameter

In this case, when eq (1) is fitted to the incidence curve, a rather poor fit is obtained, (Fig 7) In fact the equation does not seem to define the tumour incidence Neither was it possible to represent this incidence curve with GRAY's model, in view of the vagueness of the dose response of low doses

Eq (1) has been derived by means of the experimental values for the induction of

mathematical models (GRAY 1965, SPRING & PAASIKALLIO 1973) Determinations have been made of the parameter values describing the cell survival of the irradiated tissue and the two models compared

ZUSAMMENFASSUNG

Um ein Modell zu finden, welches die Wahrscheinlichkeit fur ein Rezidiv bei der Strahlentherapie beschreibt, wurden die Kurven von neun strahlenhervorgerufenen Tumorfällen zwei verschiedenen mathematischen Modellen angepasst (GRAY 1965, SPRING & PAASIKALLIO 1973) Es wurden Bestimmungen der Werte der Parameter, welche das Überleben der Zellen des bestrahlten Gewebes beschreiben, gemacht und die beiden Modelle verglichen

RÉSUMÉ

Pour trouver un modèle qui décrive la probabilité de récidive après traitement par les radiations, les auteurs ont établi neuf courbes de fréquence de tumeurs induites par les radiations au moyen de 2 modèles mathématiques différents (GRAY 1965, SPRING & PAASIKALLIO 1973) Ils ont déterminé les valeurs des paramètres qui décrivent la survie de cellules du tissu irradié et ont comparé les 2 modèles

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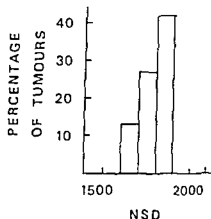


Fig. 10. The percentage distribution of laryngeal carcinoma with recurrences as a function of the NSD values (SPRING et coll. 1972).

illustrates the proportion of the irradiated area of the whole animal as a function of the product of the parameters D_0 and n, calculated by means of eq. (1). Apparently, the smaller the proportion of the irradiation field of the whole animal, the higher is the radiation dose needed to induce tumours in normal tissues. The calculations made with GRAY's model do not indicate such a straightforward relationship.

The determination of D_0 and n by GRAY's model is a rough approximation, in which the incidence curves have high threshold doses (Fig. 4), this is explicable by the lack of any dose response at low doses, which was one of the basic assumptions in derivation of the model.

Both of the models have been derived for the description of tumour induction with single doses. When patients are irradiated, the dose is almost always fractionated. In those cases, the single dose corresponding to the fractionated dose should be calculated before the application of these models.

The data in the report on the patients with laryngeal carcinoma (SPRING et coll.) have been used for comparison of the induction curves of the animal experiments and patient data.

The NSD (Nominal Standard Dose) values for each patient have been calculated by means of the Ellis formula $D = NSD\ T^{0.11} N^{0.24}$, the results obtained are expressed in Fig. 10. The percentages of patients with recurrences are drawn as a function of the NSD-values. The figure obtained rather closely resembles the induction curves obtained from animal experiments, although the points are too few to allow any fitting of either of the models.

Acknowledgement

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SUMMARY

In the search for a model that describes the probability of recurrence in radiation therapy, nine radiation induced tumour incidence curves have been fitted by means of two different

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MANTLE TREATMENT OF HODGKIN'S DISEASE

Results and side effects

GUDRUN SVAHN-TAPPER, L BALDETORP and T LANDBERG

The rationality of irradiation not only of involved but also of adjacent, clinically apparently uninvolved lymph node groups in patients with localized Hodgkin's disease has been stressed by PETERS (1950, 1966), PETERS & MIDDLEMISS (1958), KAPLAN (1962, 1966), SALZMAN et coll (1964), JELLIFFE (1965), NOBLER (1968), and others

In recent years the mantle technique has been widely used in the treatment of supradiaphragmatic disease The recommended absorbed dose in the target is usually about 40 Gy (4 000 rad) in 4 weeks, or the treatment is given in split-course with a rest interval (LANDBERG & FORSLO 1970, LANDBERG et coll 1971, JOHNSON et coll 1971, LANDBERG et coll 1973, FAZEKAS et coll 1975)

It still remains to be demonstrated if extended field treatment is superior to involved-field treatment in Hodgkin's disease Prospective trials have not demonstrated any definite superiority of either method

Since extended-field radiation therapy may carry a higher morbidity and even

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Material and Methods

The material consisted of 90 patients with supradiaphragmatic Hodgkin's disease, stages I, II, or III A, treated with the mantle technique or total nodal irradiation from 1967 to 1974

The staging procedures included as a rule lymphography, scintigraphy and percutaneous fine needle aspiration biopsy of the liver and spleen, bone marrow examination (aspiration or biopsy), chest films, and from 1971 staging laparotomy with splenectomy

In the mantle treatment the border of the target (Fig 1) is defined with the patient in treatment position at least as follows the cranial border is at the caudal border of the external auditory canals and includes the submaxillary and the submental nodes In the axillae two thirds of the humeral heads are included (the patients are treated with their arms raised) and medially the target follows the caudal border of the third rib The position of the axillary lymph nodes in a patient with raised arms has been demonstrated by KETT et coll (1970), GRANT et coll (1973) and WEISENBURGER & JUILLARD (1974) One centimeter below the clavicle is included The mediastinum is included in the mantle to the middle of the tenth vertebra, since this is usually a region where few lymph nodes are found, and thus it is a level where a gap to an abdominal field may be placed with reasonable safety In the hilar regions the ta [illegible]

[illegible] SARRAZIN et coll (1965), TAKAHASHI (1969) and with personal experience of the present authors in the postmortem room Furthermore, the definition refers to a patient without bulky disease If the patient is not safely immobilized during treatment, additional margins have to be added to the target

The irradiations were given with ^{60}Co at SSD 130 cm and with the field 1 cm outside the target area blocked near the patient The patients were irradiated in both supine and prone positions, and they were immobilized in large, individual casts, one for each position These casts immobilized the patients from the vertex to the middle of the femora and they were made to minimize changes in patient contour upon change in position from supine to prone and vice versa

Individual dose plans including correction for tissue heterogeneity were made for each patient and measurements of absorbed dose in or at the patients were performed generously Data on the technique have been presented previously (SVAHN-TAPPER 1970, 1976, SVAHN-TAPPER & LANDBERG 1971 and LANDBERG & SVAHN-TAPPER 1976) The correction for lung tissue was made according to SVAHN-TAPPER & LANDBERG and the fields were accordingly diminished over the hilar regions towards the end of treatment This was not performed in the first 10 patients treated, and these 10 thus received a relatively large absorbed dose in the hilar regions

A typical example of a slow film exposed during treatment appears in Fig 2

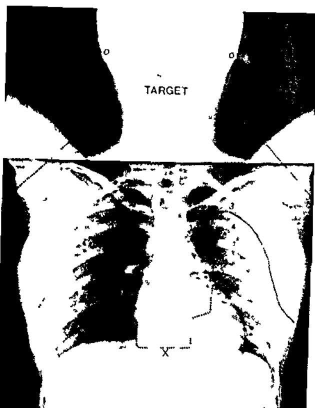


Fig 1 Example of target volume in the mantle treatment of Hodgkin's disease The minimum size of the target in the hilar region is 8–10 cm × 8–10 cm O = external auditory canal, × = tenth thoracic vertebra, 3 and 4 = third and fourth rib, respectively = border of the target



Fig 2 Example of slow film exposed during mantle treatment of Hodgkin's disease

mortality than involved-field therapy, the superiority, if any, of the former method compared with the latter may be outweighed by side effects

In 1971 a preliminary report was given of side effects and early results of mantle treatment for Hodgkin's disease from these departments (LANDBERG et coll), and in 1972 a report on the radiation sensitivity of tissues irradiated during mantle treatment of Hodgkin's disease was given (LANDBERG et coll)

The purpose of the present communication is to report results and side effects in a larger group of patients, including the previous materials

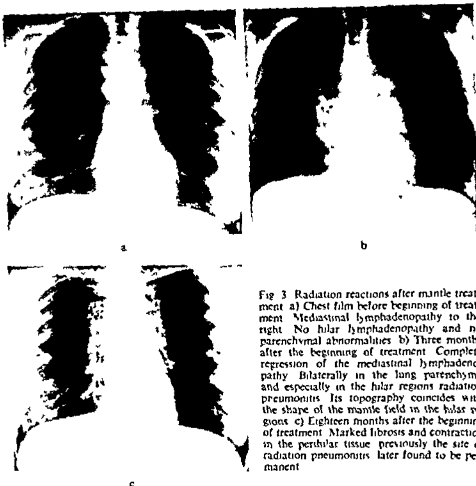


Fig 3 Radiation reactions after mantle treatment a) Chest film before beginning of treatment Mediastinal lymphadenopathy to the right No hilar lymphadenopathy and no parenchymal abnormalities b) Three months after the beginning of treatment Complete regression of the mediastinal lymphadenopathy Bilaterally in the lung parenchyma and especially in the hilar regions radiation pneumonitis Its topography coincides with the shape of the mantle field in the hilar regions c) Eighteen months after the beginning of treatment Marked fibrosis and contraction in the perihilar tissue previously the site of radiation pneumonitis later found to be permanent

$$\gamma_1(G) = \left(\frac{T+G}{T}\right)^{0.11}$$

(WINSTON et coll 1969) where $\gamma(G)$ = fractional decay of the CRE during the gap, G is the gap-time in days, and T is the time in days for the first series (course) of treatment and according to the formula

$$\gamma_2(G) = e^{0.009G}$$

(KIRK et coll 1975)

In some patients abnormalities in the heart and pericardium were observed, which were considered to be compatible with radiation reactions Usually they did *not* give any symptoms, and only appeared on chest films (Fig 4) For the heart and pericardium the absorbed dose at a depth of one third of the antero-posterior distance

An absorbed dose of 40 Gy (4 000 rad) in the target, confirmed by in vivo measurements, and delivered with 5 fractions per week was aimed at Usually the target absorbed dose per fraction was of the order of 1 5 Gy (150 rad) and as a rule split-course treatment was used with two thirds of the total absorbed dose in the first series and an interval of 4 weeks between the two series Thus 40 Gy in 27 fractions over 71 days was usually given

In the present material 2 fields were irradiated per fraction in 27 patients, 1 field per fraction in 53 patients and in 10 patients 1 field was irradiated per fraction for approximately half of the total course and 2 fields per fraction during the remaining course The reason for this was varying patient load on the treatment apparatus

After end of treatment the patients were seen regularly In case of complete remission no chemotherapy was given, and the patients were seen every third month the first year, every fourth month the second year, and then twice a year The follow-up examinations included chest films

At review of the patients' charts special attention was focused on relapsing disease or side effects of the irradiation in the lungs, heart and pericardium, or spinal cord

As suggested by KAPLAN (1966), local recurrence may be either a true recurrence or a marginal recurrence, being the first new sign of disease after primary treatment, whereas extension means a new manifestation of disease outside the irradiated tissues

When evaluating the side effects of mantle treatment, symptoms or signs found 1, 3, and 6 months or more after the beginning of therapy were noted Patients were considered evaluable only if they had a follow-up of at least 6 months Only patients treated with split-course therapy were included Symptoms and signs of radiation reactions in the lung parenchyma, heart and pericardium, and spinal cord as a rule showed a 'peak reaction' and then gradually improved In the analysis, the peak reaction was recorded as the representative one

Some patients had no symptoms of radiation pneumonitis, but in some of these, slight abnormalities were found on chest films Other patients had moderate symptoms of radiation pneumonitis (slight cough, slight fever) which were not considered so severe as to merit specific therapy, or moderate abnormalities on chest films (Fig 3) This figure illustrates a typical reaction of moderate degree following mantle treatment In still other patients severe symptoms of radiation pneumonitis occurred, necessitating therapy with broad spectrum antibiotics and steroids, and with marked pulmonary abnormalities on chest films

For each patient the maximum absorbed dose in the midplane of the hilar regions was calculated, i e the region where radiation pneumonitis was most extensive on chest films

The doses were corrected for lung tissue using the diagram published by SVAHN-TAPPER & LANDBERG The Cumulative Radiation Effect (CRE) value was calculated with gap correction both according to the formula

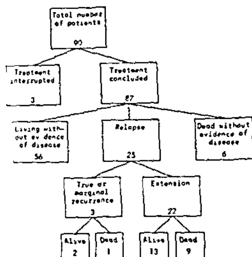


Fig 5 Results of mantle treatment for supradiaphragmatic Hodgkin's disease, Lund 1967–1974

was chosen as the representative one For the patients with only one field irradiated per fraction the 'effective dose' per fraction was calculated according to KIRK et coll (1971) from the formula

$$d=\left(\frac{d_a^{1/m}+d_b^{1/m}}{2}\right)^m$$

where d = effective dose per fraction, d_a and d_b = absorbed dose from fields Nos 1 and 2, respectively, and m = 0 65 The gap correction was calculated according to WINSTON et coll

At follow-up the patients had been asked for symptoms suggestive of radiation myelitis or Lhermitte's sign The maximum absorbed dose in the whole spinal cord was recorded as the representative absorbed dose for the cord In the present material no shield for the spinal cord had been used

Results

The treatment was concluded in 87 of the 90 patients (Fig 5) Fifty-six are alive without evidence of disease, 25 have relapsed, and 6 have died without known extension of disease Data on the final course of these 6 patients are scarce, and it cannot be

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Fig 4 (For legend see opposite page)

Table 2

Rad ation pneumonitis or fibrosis in 80 patients treated with split-course mantle treatment for Hodg kin s disease and followed up for at least 6 months

	Number of patients	Age (range median mean and SD)	Number of patients with mediastinal lymph adenopathy	Treatment data for the hilar regions (range median mean and SD)					
				Absorbed dose (Gy)	Number of fractions	Number of days	CRE value of first series	CRE value of full treatment *	CRE value of full treatment **
Neither symptoms nor signs	17	7 54 26 27 11	4	37–46 41 5 42 2 35	20–44 27 28 5	54 93 72 72 11	710 1 367 973 989 142	1 148 1 438 1 211 1 221 71	1 025 1 217 1 095 1 102 62
No symptoms slight radiologic abnormalities	22	7–67 27 33 17	6	39–45 41 41 5 1 60	23 36 26 27 3	56–96 71 70 9	800 1 139 988 994 108	1 110–1 389 1 20 1 231 74	982 1 289 1 108 1 120 88
Moderate symptoms or moderate radiologic abnormalities	14	6–58 30 32 16	6	37–46 5 41 25 41 45 2 3	23–40 27 27 4	53 97 76 73 11	684 1 181 1 010 992 121	1 043 1 342 1 232 1 211 83	957 1 204 1 105 1 093 79
Marked symptoms or extensive radiologic abnormalities	27	16 71 35 37 17	15	38–49 41 5 42 45 2 5	21 31 27 27 3	51 80 70 68 7	812 1 177 1 027 1 031 77	1 164 1 470 1 241 1 257 62	1 059 1 360 1 139 1 143 66

* Gap calculated according to WINSTON et coll (1969)
** Gap calculated according to KIRK et coll (1975)

well be labelled a marginal one It occurred just below the external auditory canal Analysis in retrospect of the repeated measurements of absorbed dose in the external auditory canal showed that in the first series abnormally low values had been recorded whereas the upper margin of the field seemed to have been more properly adjusted in the second series

Of patients with a local recurrence 2 (Nos 22 and 43) are still alive Patient No 69 died from generalized disease he also developed acute myeloid leukemia

Radiation pneumonitis or fibrosis Eighty patients treated with split-course radiation therapy and followed for at least 6 months were evaluated (Table 2) Seventeen

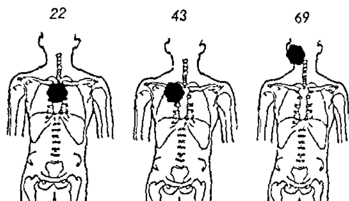


Fig 6 Sites of true or marginal recurrences in 3 out of 87 patients after mantle treatment for Hodgkin's disease

decided if death was due to progressive disease or to other causes Of the 25 patients with relapse, 3 recurred locally and 22 had extensions Fifteen of the 25 are still alive

No local recurrence Fifty-four patients treated with split-course treatment stayed symptom-free after the initial treatment (Table 1) The absorbed dose in the target for these patients ranged between (mean values) 43 2 Gy (4 320 rad) maximum target dose, and 37 65 Gy (3 765 rad) minimum target dose, the mean absorbed minimum dose in demonstrable tumour being 40 30 Gy (4 030 rad) The irradiations had been given in mean 27 fractions in mean 71 days The follow-up for these 54 patients ranged from 9 to 87 months with a mean of (38 ± 20) months

Local recurrence A true or marginal recurrence was observed in 3 of 87 patients (3 per cent, Fig 6), in 2 patients in the superior mediastinum (Nos 22 and 43) 5 months after mantle treatment The absorbed dose in these two sites had been 38 5 and 40 Gy, respectively There is no other explanation for the relapse in one of these patients (absorbed dose = 38 50 Gy) than a true recurrence, but the local recurrence in patient No 43 may well have been a marginal recurrence, and the corresponding absorbed dose may then have been smaller than 40 Gy The recurrence occurred in the region of the medial part of the clavicle The recurrence in patient No 69 may

Table 1

Absorbed dose in 54 patients being alive and without evidence of disease after split course mantle treatment for Hodgkin s disease

	Maximum target absorbed dose (Gy)	Minimum absorbed dose in demon strated tumour (Gy)	Minimum target absorbed dose (Gy)	Number of fractions	Number of days	Follow up (months)
Range	39–48	32–44 5	29 5–42	20–44	51 93	9–87
Mean	43 20	40 30	37 65	27	71	38
SD	1 95	2 15	2 45	4	9	20

Table 4

Radiation reactions of the spinal cord in 80 patients treated with split-course mantle treatment for Hodgkin's disease and followed up for at least 6 months

	Number of patients	Age (range mean and SD)	Treatment data for the spinal cord (range mean and SD)		
			Absorbed dose (Gy)	Number of fractions	Number of days
Neither symptoms nor signs	73	6–71	35–48	20–44	51 97
		33	42	27	71
		17	1 96	4	10
Lhermitte's sign	7	18 50	40 5–44	24 31	60–78
		30	42 50	26	68
		10	1 08	3	8

Radiation myelitis Seventy three of 80 patients had no symptoms or signs of radiation myelitis (Table 4) 7 had Lhermitte's sign, but no patient had any serious reaction from the cord The absorbed dose in the cord had been of the order of 42 Gy in 27 fractions in 70 days, and no dose difference existed between patients with and patients without Lhermitte's sign Age did not seem to be of importance All patients with Lhermitte's sign had one field irradiated per fraction Six have not received chemotherapy whereas in one patient chemotherapy with MOPP was started 6 months after the beginning of mantle treatment at the same time as Lhermitte's sign appeared

Other tumours It may be mentioned that out of the 90 patients, 6 have had other tumours before or after the mantle treatment Three patients had been treated for a tumour before mantle treatment (one for intrathoracic fibroxanthoma one for car- [illegible]

[illegible] latter patient had received both total nodal irradiation and chemotherapy)

Discussion

Local recurrence It is generally recognized that 40 Gy (4 000 rad) is an absorbed dose that gives local control in Hodgkin's disease in a reasonably high frequency (KAPLAN 1966) It has been shown (LANDBERG & FORSLO JOHNSON, LANDBERG et coll 1973) that the total time is not very critical, and the treatment may well be extended over a relatively long period of time, a fact that was also stressed by KAPLAN He considered 4 000 rad given with 1 000 rad per week to give local control in 95 per cent of lesions The remaining 5 per cent that failed to be controlled may be regarded

Table 3

Radiation reactions in the heart and pericardium in 80 patients treated with split course mantle treatment for Hodgkin's disease and followed up for at least 6 months

	Number of patients	Age (range, mean, and SD)	Treatment data for the central part of the heart (range, mean, and SD)			
			Absorbed dose (Gy)	Number of fractions	Number of days	CRE value
Neither symptoms nor signs	72	6–69	35–46	20–44	51–97	998–1 320
		31	40 6	27	71	1 196
		15	2 07	4	10	71
Symptoms or signs	8	20–71	39–43	22–30	57–72	1 026–1 277
		45	40 1	26	67	1 200
		20	3 02	2	5	84

patients had neither symptoms nor signs of pulmonary radiation reactions, 22 had no symptoms but slight abnormalities on chest films, 14 had moderate symptoms or moderate abnormalities on chest films, and 27 had severe symptoms or extensive abnormalities on chest films The four groups of patients appear in Table 2, distributed on age, frequency of mediastinal involvement, absorbed dose (in Gy) in the hilar regions, number of fractions and days, and CRE value of absorbed dose in the hilar regions in the first series and calculated with gap correction both according to WINSTON et coll and KIRK et coll (1975), respectively, for the whole treatment No evident differences exist, but some tendencies may be noted Pulmonary radiation reactions seemed to increase with age of the patient and frequency of mediastinal lymphadenopathy, and the most severe reactions occurred at dose levels slightly higher than in patients without reaction The presence of hilar lymphadenopathy, (totally 13 patients) cannot explain the occurrence of pulmonary radiation reactions No difference in frequency of pulmonary radiation reactions was found between patients with only one field irradiated per fraction and those with 2 fields irradiated per fraction

Radiation reactions of the heart and pericardium Symptoms or signs of radiation carditis or radiation pericarditis were observed in 8 out of 80 evaluated patients (Table 3) The patients with demonstrable reactions were older, but no difference could be found as regards absorbed dose given or fractionation between patients with and patients without radiation carditis or radiation pericarditis Of the 8 patients with radiation heart reaction, 2 had one field irradiated per fraction and 6 had 2 fields irradiated per fraction

It may be mentioned that reactions were as a rule slight and did in no instance necessitate pericardial tapping or pericardiectomy

part of the infraclavicular fossa rather caudally Shielding in this region may be hazardous

The low frequency of local recurrence in the present material (about 3 per cent) indicates that it is quite safe to use split-course treatment with an absorbed dose in the target of 40 Gy given in 27 fractions in two series over totally 10 weeks

Retreatment of a local recurrence has usually been successful only in the hilar region, and RUBIN et coll (1974) stated that 'the initial management decision at the time when the patient is first seen is the most critical if cure is to be achieved by irradiation

Lung tissue In a previous report (LANDBERG et coll 1971) a detailed description was given of radiation effects of the lung tissue, heart and pericardium of 12 of the patients in the present material Lung function examinations indicated that there was only a relatively slight decrease in the spirometric values The ECG was normal in all but one patient, who had an S R ratio of more than 1 0, this patient also had tachycardia

In most of the present patients no prospective lung function examinations were performed

Radiation reactions of the lung tissue, heart and pericardium proved not to be of any serious significance though transient symptoms of radiation pneumonitis were often relatively severe

The frequency of radiation pneumonitis and radiation lung fibrosis has been the subject of numerous reports (COULTER et coll 1972, LIBSHITZ et coll 1973, HOST & VALE 1973, LOKICH et coll 1973, EVANS et coll 1974) Since it is rarely if ever demonstrated how much lung tissue that was included in the mantle field or whether the absorbed doses reported have been corrected for tissue heterogeneity, it is difficult to make a meaningful pooling of the dose response relationship of the lung tissue in mantle treatment of Hodgkin s disease

COULTER et coll reported on lung function analyses in 89 patients after mantle treatment for Hodgkin s disease Two patients died of pulmonary insufficiency and cor pulmonale Other pulmonary complications were tracheooesophageal fistula, pneumothorax and atelectasis Forty four per cent of the patients were asymptomatic

LIBSCHITZ et coll reported on 20 patients, 19 with radiation lung fibrosis, and 13 with radiation pneumonitis The authors concluded that there is a time dose relationship of the pulmonary parenchymal radiation reactions Two of their patients also had radiation pericarditis

HOST & VALE reported lung function examinations in 17 patients after mantle treatment The vital capacity was reduced at the end of treatment with on the aver age 10 per cent No influence on the pulmonary gas exchange could be demonstrated

LOKICH et coll found that the diffusing capacity may be reduced already before irradiation, and patients with intrathoracic Hodgkin's disease had lower pulmonary

as extremes in the biologic variation in radiation sensitivity of Hodgkin's disease It may also be that some of the local recurrences labeled as true recurrences in fact are marginal ones, since the frequency of uncontrolled lesions seems to increase rapidly with decreasing dose (KAPLAN 1966), and it is well known that often radiation therapy of such a complex nature as the mantle treatment may be prone to poor reproducibility in treatment set up MARKS et coll (1974) have for example reported on localization error in the irradiation of Hodgkin's disease and the non-Hodgkin's lymphomas They found in 99 patients treated with the mantle technique 10 local recurrences (6 in the axilla, 2 in the neck, and 2 in the mediastinum) and could often explain by means of serial slow films these recurrences on the basis of underdosage

The literature contains only few reports on the frequency of recurrences after mantle treatment with an adequate notation of absorbed dose in Hodgkin's disease

MARYUAMA & KAHN (1971) found 12 patients of 36 to have local recurrences after 3 500 rad in 3 weeks Eight recurrences occurred in the hilar regions, 2 in the axillae, 2 in the supraclavicular region, 4 in the submaxillary or preauricular region, and one recurrence was observed at the level of the suprasternal notch between two hemimantle ports The authors discussed possible ways to diminish the high frequency of local recurrence by means of different techniques

RUBIN et coll (1969) reported 11 local recurrences in 65 patients after mantle treatment, and 12 patients with local recurrence out of 83 treated (RUBIN et coll 1974) Nine of these recurrences were localized to one nodal region and the other 3 presented at more than one nodal site There were 4 recurrences in the hilar nodes, 7 recurrences in the neck nodes, 4 in the axillary nodes and 2 in the epitrochlear nodes Approximately half of the local recurrences were considered to be marginal ones MARKS et coll (1974) reported 8 local recurrences in 68 patients

FAW et coll (1971) found only one local recurrence in 80 patients, and FAZEKAS et coll reported 3 local recurrences in 83 patients, the absorbed dose in the two series having been 4 000 rad and 3 600 to 4 400 rad, respectively

Most of the local recurrences reported have occurred in the hilar and the submaxillary regions Attempts to diminish the frequency, severeness, and seriousness of radiation pneumonitis may well counteract attempts to deliver a tumoricidal absorbed dose in the hilar regions Recurrences in the submaxillary region are probably often due to faulty immobilization of the patient or simply to the fact that the field border was placed too caudally in order to avoid dryness of the mouth A rather interesting site for recurrence is medially in the infraclavicular fossa This seems not to have attracted much attention, though 2 such recurrences were reported by ROSENBERG & KAPLAN (1966) in 20 patients treated with the mantle technique One of the patients in the present material demonstrated a recurrence in a position corresponding to the medial part of the infraclavicular fossa and upper mediastinum The occurrence of infraclavicular chest wall tumours in Hodgkin's disease was reported in 6 of 91 patients by GOLDMAN (1952), and FUCHS (1969) has shown on lymphography that lymph nodes may fill up in a site that corresponds to the medial

part of the infraclavicular fossa rather caudally Shielding in this region may be hazardous

The low frequency of local recurrence in the present material (about 3 per cent) indicates that it is quite safe to use split-course treatment with an absorbed dose in the target of 40 Gy given in 27 fractions in two series over totally 10 weeks

Retreatment of a local recurrence has usually been successful only in the hilar region, and RUBIN et coll (1974) stated that 'the initial management decision at the time when the patient is first seen is the most critical if cure is to be achieved by irradiation'

Lung tissue In a previous report (LANDBERG et coll 1971) a detailed description was given of radiation effects of the lung tissue, heart and pericardium of 12 of the patients in the present material Lung function examinations indicated that there was only a relatively slight decrease in the spirometric values The ECG was normal in all but one patient, who had an S R ratio of more than 1 0, this patient also had tachycardia

In most of the present patients no prospective lung function examinations were performed

Radiation reactions of the lung tissue, heart and pericardium proved not to be of any serious significance, though transient symptoms of radiation pneumonitis were often relatively severe

The frequency of radiation pneumonitis and radiation lung fibrosis has been the subject of numerous reports (COULTER et coll 1972, LIBSHITZ et coll 1973, HOST & VALE 1973, LOKICH et coll 1973, EVANS et coll 1974) Since it is rarely if ever demonstrated how much lung tissue that was included in the mantle field or whether the absorbed doses reported have been corrected for tissue heterogeneity, it is difficult to make a meaningful pooling of the dose-response relationship of the lung tissue in mantle treatment of Hodgkin's disease

COULTER et coll reported on lung function analyses in 89 patients after mantle treatment for Hodgkin's disease Two patients died of pulmonary insufficiency and cor pulmonale Other pulmonary complications were tracheooesophageal fistula, pneumothorax, and atelectasis Forty-four per cent of the patients were asymptomatic

LIBSCHITZ et coll reported on 20 patients, 19 with radiation lung fibrosis, and 13 with radiation pneumonitis The authors concluded *that there is* a time-dose relationship of the pulmonary parenchymal radiation reactions Two of their patients also had radiation pericarditis

HOST & VALE reported lung function examinations in 17 patients after mantle treatment The vital capacity was reduced at the end of treatment with on the average 10 per cent No influence on the pulmonary gas exchange could be demonstrated

LOKICH et coll found that the diffusing capacity may be reduced already before irradiation, and patients with intrathoracic Hodgkin's disease had lower pulmonary

indices which improved with tumour resolution Total lung capacity and inspiratory capacity were maximally affected at 9 months but returned towards normal by 24 months Similar findings were noted by EVANS et coll

BORGNES & HATLEVOLL (1971) reported on lung complications in a series of 70 patients One third of the patients had no radiologic lung abnormalities Two patients died from respiratory insufficiency and cor pulmonale

PATERSON (1963) recommended 3 000 rad in 3 weeks as an upper dose limit for any major irradiation of lung parenchyma This dose limit corresponds to a CRE value of 1 150 If the entire lungs and the mediastinum are irradiated, the same author puts the limit at 2 500 rad, which when given in 3 weeks corresponds to a CRE value of 950

With the mantle fields used in the present material about one third to half of all lung tissue was irradiated to an absorbed dose of about 40 Gy The rest of the lungs received a dose of 4 to 7 Gy (400 to 700 rad) from scattered radiation and primary radiation through the lung blocks With gap correction according to WINSTON et coll (1969) this is equivalent to a CRE value of 1 225, and with gap correction according to KIRK et coll (1975) it is equivalent to a CRE value of 1 100 For the irradiated volume and the time-dose schedule usually used in the present material these figures seem to represent a borderline region between negligible and serious lung reactions and thus may represent the tolerance limit for the lung tissue in mantle treatment

Heart and pericardium Radiation reactions of the heart and pericardium have been reported to occur with various frequency and different grade of severity and seriousness BYHARDT et coll (1975) reported radiation-related pericardial effusion in 24 out of 83 patients treated with the mantle technique for Hodgkin s disease In 4, surgical procedures proved necessary The average midplane cardiac absorbed dose in the whole series corresponded to a Nominal Standard Dose (NSD, ELLIS 1969) value of 1 558, and the pericardial dose to a NSD value of 1 823 No obvious correlation between any value of NSD and the occurrence of cardiac or pericardial reactions could be demonstrated

Other reports (COHN et coll 1967, STEWART et coll 1968, FAJARDO et coll 1968) have indicated that there may be a rather evident dose-limit for radiation reactions of the heart and pericardium, corresponding an NSD value of 1 500–1 850 depending on the size of the irradiated tissue concerned In the present series of patients, in whom the cardiac dose corresponded in general to a CRE value of about 1 200, radiation reactions of the heart and pericardium had no serious clinical significance Pericardial effusion did not occur In some of the patients the transverse cardiac diameter decreased as reported previously by PIERCE et coll (1969)

Spinal cord In the present material no serious symptoms of radiation myelitis were encountered A few patients had a moderate Lhermitte's sign

Other tissues It may further be mentioned that since the upper border of the field had been placed rather high cranially to secure an adequate absorbed dose in the lymph nodes at the tip of the mastoid, it had not been possible to avoid irradiation of much of the salivary glands The patients therefore have usually experienced a dry mouth and in about 10 per cent dental decay has occurred The symptoms of dry mouth have usually diminished over a rather protracted period of time, often lasting for up to 2 years The patients have been checked for thyroid insufficiency, and thyroid substitution has proved necessary in some patients Subcutaneous fibrosis in mainly the neck and supraclavicular region has occurred in some patients, but was clinically of no serious significance

In a previous report (LANDBERG et coll 1972) a review was given of the radiation sensitivity of tissues irradiated during mantle treatment of Hodgkin's disease It was concluded that the irradiation may with advantage be extended over a relatively long period of time in order to minimize the risk for radiation reactions of healthy tissues The present results confirm this opinion With the technique used the main untoward reactions have been pulmonary radiation reactions and a dry mouth whereas minor reactions have been encountered from the heart and pericardium or the spinal cord In general younger persons seemed to tolerate the treatment better than old ones

SUMMARY

Eighty seven patients were treated with the mantle technique for Hodgkin s disease Usually 40 Gy in 27 fractions in two series over 71 days were given A local recurrence was diagnosed in 3 of 87 patients An analysis of radiation reactions of the lung tissue, heart and pericardium and spinal cord is reported It is recommended to give mantle treatment for Hodgkin s disease over a relatively long period of time such as in split-course in two series

ZUSAMMENFASSUNG

Siebenundachtzig Patienten mit Hodgkin scher Erkrankung wurden mit der Manteltechnik behandelt Gewohnlich wurden 40 Gy in 27 Fraktionen in zwei Folgen während 71 Tage verabfolgt Lokale Rezidive wurden bei 3 von 87 Patienten diagnostiziert Es wird ... eine Analyse der ...
des Ruckenmarke ...
kin schen Erkrank ...
lung in zwei Absc ...

RÉSUMÉ

Quatre vingt sept malades ont été traités par la technique en mantelet pour maladie de Hodgkin Le plus souvent on a administré 40 Gy en 27 fract ...

et de la moelle épinière Ils recommandent d'administrer le traitement en mantelet pour la maladie de Hodgkin sur une période de temps relativement longue comme un split-course en deux séries

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BIOPSY OF THE NASOPHARYNX AS A STAGING PROCEDURE IN HODGKIN'S DISEASE

A BJÖRKLUND, EVA CAVALLIN STÅHL, T LANDBERG, L G LINDBERG and M ÅKERMAN

The remarkable progress achieved during the last decade in the treatment of Hodgkin's disease is the result of a more precise mapping of the extension of the disease and better therapeutic means. By use of lymphography and staging laparotomy silent involvement of abdominal tissues have frequently been revealed during the primary staging of patients.

Most patients with Hodgkin's disease have cervical lymphadenopathy at presentation. These nodes drain also the nasopharynx. However, reports on early involvement of the nasopharynx in Hodgkin's disease are scarce.

The present report gives the results of epipharyngoscopy in 76 previously untreated patients with Hodgkin's disease.

Material and Methods. During the years 1969 to 1975 totally 180 patients with Hodgkin's disease were seen at this hospital. The patients were staged according to the Ann Arbor system (Ro...
lymphography and l...
examination was per... ...uced inspection of the nasal cavity and the

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Table 1

Microscopic type of lymph node biopsy in 45 patients

Microscopic type	Biopsy of the nasopharynx		
	Positive	Suggestive	Negative
Lymphocyte predominance	0	3	6
Mixed cellularity	3	0	17
Lymphocyte depletion	0	0	2
Nodular sclerosing type	1	0	13

laryngeal and pharyngeal spaces by a senior member of the ENT-staff. In 45 of these patients a biopsy was made from the nasopharyngeal region. In the remaining 104 patients no detailed ENT-examination was performed, the main reason being either advanced stage of disease or the fact that the patients had been staged and treated at other hospitals.

On the lying patient, the nasal cavities and the pharynx were anaesthetized with local anaesthesia, the head was tilted backwards and the epipharyngeal region inspected by a mirror. The biopsy forceps were introduced either through the nasal cavity or the pharynx, and the biopsy was made either from areas considered to be abnormal or from seemingly normal mucosa.

Microscopic classification of the initial lymph node biopsies was made according to LUKES et coll. (1966) and LUKES & BUTLER (1966). All epipharyngeal specimens were compared with the microscopic appearances of the initial lymph node biopsy. The presence of Reed-Sternberg cells or Hodgkin cells was considered necessary for a diagnosis of nasopharyngeal involvement. In some patients a conclusive microscopic diagnosis of nasopharyngeal involvement could not be achieved but the appearance was clearly abnormal with large mononuclear cells of histiocytic type and disarranged lymphatic tissue. These changes were considered a suggestive, but not a definite proof of involvement.

The analysis of the series was restricted to the 45 patients with biopsy of the nasopharynx, 34 were males and 11 females, the age ranged between 16 and 80 years with a mean of 41.

Results

At microscopy, typical abnormalities in the nasopharyngeal specimen indicating Hodgkin's disease were found in 4 patients and in a further 3 patients the findings were abnormal and suggestive of this disease. In 38 patients the microscopy was normal. Thus, in 7 of 45 (16 %) patients abnormalities were revealed that either necessitated therapy or repeat examination.

Table 2

Stage before epipharyngoscopy in 45 patients

Stage before epipharyngoscopy	Biopsy	
	Positive or suggestive	Negative
1	2	14
2	3	8
3	1	11
4	1	5
No symptoms	5	26
Symptoms of systemic disease	2	12

Table 3

Signs of ENT involvement in 45 patients

Findings at epipharyngoscopy	Biopsy	
	Positive or suggestive	Negative
Normal	2	27
Swollen or adenoid like	3	9
Granulated	1	2
Tumour	1	0
Total	7	38

The microscopic type of the lymph nodes on different groups of patients appears in Table 1 Of the 4 patients with a positive nasopharyngeal biopsy, 3 displayed mixed cellularity and one was of the nodular sclerosing type, whereas in all 3 patients with a non conclusive, but possibly pathologic nasopharyngeal specimen, a lymphocyte predominance was observed in the initial lymph node biopsy The 38 patients with a negative nasopharyngeal biopsy are distributed among the different microscopic types usually found at this hospital

The stage before epipharyngoscopy for patients with positive or suggestive nasopharyngeal biopsy and for those with a negative biopsy appears in Table 2 The patients with a positive or suggestive biopsy were usually in an early stage, whereas this was not evident for patients with a negative biopsy The two groups did not differ as regards the presence or absence of symptoms of a systemic disease

Only one of the 7 patients with positive or suggestive biopsy had local symptoms, presenting as an otosalpingitis The remaining 6 had no local symptoms, as was the case with the 38 patients with a negative biopsy Local ENT signs are given in Table 3

Table 4

Sites other than nasopharynx involved at presentation in 45 patients

Sites	Biopsy	
	Positive or suggestive	Negative
Other ENT-sites	1*	1**
Cervical lymph nodes		
Cranially only	2	5
Caudally only	0	11
Cranially and caudally	3	13
No cervical lymph nodes	2	9
Outside the head and neck region	4	29

* Tonsil

** Tonsil and parotid gland

Of the 4 patients with a positive biopsy, two had a normal, one a swollen or adenoid-like, and one a granular appearance of the nasopharynx at epipharyngoscopy Of the 3 patients with abnormalities suggestive of Hodgkin's disease, two had an adenoid-like appearance and one a tumour

The sites involved at presentation appear in Table 4 and for each of the 7 patients with abnormal biopsy in Table 5 In patient number 3 only the axilla was involved in addition to the nasopharynx In this case the nasopharynx appeared macroscopically normal

Thus, histologic type, stage of disease, presence or absence of symptoms and signs of involvement of the nasopharynx, or general presentation of disease, did not select patients with abnormal from those with normal biopsy of the nasopharynx

Discussion

Contrary to observations in other malignant lymphomas, the involvement of Waldeyer's lymphoid ring including nasopharynx seems to be rare in Hodgkin's disease as judged from the previous literature ENNUYER et coll (1961) gave synopses of 7 patients in the literature from the years 1927 to 1958 with nasopharyngeal involvement, but reported no case of their own KAPLAN (1972) stated that there is a remarkably low frequency of involvement of the tonsil and the lymphatic structures of Waldeyer's ring in this disease and, that, when it occurs, it is usually associated with involvement of the upper cervical and sometimes the preauricular lymph nodes TODD & MICHAELS (1974) reported on 16 patients with Hodgkin's disease involving the lymphoid ring of Waldeyer, 8 had involvement of the nasopharynx, 7 of the tonsil, and one of the posterior pharyngeal wall At the time of diagnosis, 2 of the 8 with nasopharyngeal involvement had this site affected as sole manifestation, whereas

Table 5

Sites involved at presentation in 7 patients with pathologic biopsy from the nasopharynx

Sites	Patient number						
	1	2	3	4	5	6	7
	Biopsy positive				Biopsy suggestive		
Other ENT-sites					+*		
Cervical lymph nodes							
Cranially only		+					+
Caudally only							
Cranially and caudally	+			+	+		
No cervical lymph nodes			+			+	
Outside the head and neck region	+		+**		+	+	

* Tonsil
** Axilla only

the remaining 6 had more widespread disease In 7 of the 8 mixed cellularity was found and in one lymphocyte predominance

In the present prospective series the frequency of abnormal microscopic findings in the nasopharynx at the primary staging is high (16%) compared with previous reports Some of the examiners did not always perform a biopsy in patients with a normal appearance at epipharyngoscopy If the present series is taken to include all 76 patients with a detailed ENT-examination, the frequency of proven microscopic abnormalities in the nasopharynx will still be high (7/76, 9%) No simple explanation of the discrepancy between the present findings and those previously reported seems to exist One explanation may be that the nasopharyngeal involvements in the present series represent early involvement Previous reports (GHOSSEIN & NAJJAR 1967), are usually considering symptom giving involvement There seems to be no other series where biopsy of the nasopharynx has been performed as part of the primary staging procedures in Hodgkin s disease Apparently the institution of chemotherapy for relapsing disease may conceal any involvement of the nasopharynx Such relapsing disease may be due to re-seeding from an undiagnosed involvement of the nasopharynx, and this was actually seen in one of the patients in the present series, where a nasopharyngeal involvement was not established initially but only at review of the original nasopharyngeal biopsy

Neither the microscopic appearance of the lymph node biopsy, stage of disease, presence or absence of symptoms and signs of ENT-involvement, nor the general presentation of the disease did indicate nasopharyngeal involvement It is obvious that merely an inspection of the nasopharynx in order to detect early involvement is not sufficient The ENT-examination should be performed by an experienced ex-

aminer, who must obtain adequate biopsy specimens The biopsy should be directed not only towards possibly pathologic areas but also *include seemingly normal mucosa* In general, it is difficult *to evaluate small fragmented pieces of tissue from the* naso pharynx *microscopically This is especially* true if the microscopic type of disease is lymphocyte predominance, where diagnostic cells might be scarce

In conclusion, a generous biopsy of the nasopharynx is recommended to be in cluded in the pretherapeutic staging of patients with Hodgkin's disease

SUMMARY

Biopsy of the nasopharynx was performed in 45 patients with Hodgkin s disease as part of the pretherapeutic staging Seven of the 45 (16%) had microscopic abnormalities in the nasopharynx compatible with Hodgkin s disease Such abnormalities occurred even in the absence of local ENT symptoms or signs and they could not be predicted from the micro *scopic* type of *lymph* node biopsy *stage* of disease or general presentation A generous biopsy of the nasopharynx is recommended to be included in the staging procedures in *Hodgkin s disease*

ZUSAMMENFASSUNG

Biopsien des Nasopharynx wurden bei 45 Patienten mit Hodgkin scher Erkrankung als Teil der pratherapeutischen Stadieneinteilung vorgenommen Sieben der 45 Patienten (16%) hatten mikroskopische Veranderungen im Nasopharynx die mit einer Hodgkin scher Er krankung vereinbar waren Derartige Veranderungen traten auch in Abwesenheit lokaler ENT Symptome oder Zeichen auf und liessen sich nicht vom mikroskopischen Typus der *Lymphknotenbiopsie dem Stadium der Erkrankung oder dem Allgemeinbild* vorhersagen Es wird empfohlen bei den Verfahren zur Stadieneinteilung der Hodgkin schen Erkrankung *eine grosszugige Biopsie* des Nasopharynx *mit einzubeziehen*

RESUMÉ

Une biopsie du nasopharynx a été faite chez 45 malades atteints de maladie de Hodgkin comme élément de la determination préthérapeutique du stade Dans sept cas sur 45 (16%) il y avait des *anomalies microscopiques du nasopharynx compatibles* avec le diagnostic de maladie de Hodgkin Des anomalies semblables existaient meme en l absence de signes *fonctionnels ou physiques oto rhino laryngologiques locaux* elles n avaient pas pu être
d après
les tech

pharynx

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FROM ONCOLOGICAL INSTITUTE CLUJ-NAPOCA, (DIRECTOR PROFESSOR I. KIRICUTA), CLUJ, RUMANIA

TELECOBALT THERAPY FOR MALIGNANT LUNG TUMOURS

N. GHILEZAN, N. MILEA and S. TAMBURLINI

Malignant lung tumours are still a challenge for the therapist, particularly because the diagnosis is often made at a very late stage. Generally, the patients referred for radiation therapy are too advanced for surgery, but hope should not be abandoned as a fair chance remains of palliation with chemotherapy. The results of radiation therapy in this heterogeneous group of patients are poor but many long term survivals have been reported in the literature and many authors defend the usefulness of irradiation (BLOEDORN et coll. 1962, HUSTU & NICKSON 1964, DEELEY 1973, MOSS and coll. 1973). *The experience at this unit is presented in this report.*

Material

During the period from 1967 to 1971, 194 patients with malignant lung tumours were irradiated. The sex and age distribution agreed with published data (Table 1): 176 males and 18 females (ratio 10 : 1) with the highest incidence between 51 and 60 years.

The microscopic diagnosis was of squamous cell carcinoma in 29.8 per cent, undifferentiated 'oat cell' carcinoma in 26.2, adenocarcinomas in 2.5 and unspecified malignant tumours in 41.2 per cent. This latter group included all cases with malignant cytology but *without well defined histology, very advanced cases in which the diag-*

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Table 1

Malignant lung tumours in 194 patients Distribution by microscopy, age and sex

Microscopy	30 years		31–40		41–50		51–60		61–70		71		Total			
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	No of cases	Per cent
Squamous cell carcinoma			5	3	13	1	27		8		1		54	4	58	29 8
Adenocarcinoma					2		2	1					4	1	5	
Undifferentiated carcinoma	2		10	2	7	1	18		9	1	1		47	4	51	26 2
Other types			2	2	15	2	23	4	23	1	8		71	9	80	41 2
Total	2		17	7	37	4	70	5	40	2	10		176	18	194	

Table 2

Malignant lung tumours in 194 patients The 3-year survival in relation to the TNM staging

Microscopy	Tumour			Regional lymph nodes			Distant metastases			Fever	Total	
	1	2	3	0	1	2	0	1	2		No of cases	Per cent
Squamous cell carcinoma	—	4/43	1/15	—	4/25	1/33	5/41	0/7	0 10	0 19	5/58	8 6
Adenocarcinoma	—	1/3	0 2	—	1/4	0 1	1/2	—	0 3	0 1	1/5	20
Undifferentiated carcinoma	—	2/20	0 31	—	0 13	2 38	2/34	0/9	0 8	0 27	2/51	3 9
Other types	—	4/52	5/28	—	5/35	4 45	8/52	0 7	1/21	0 31	9 80	11.2
Total		11/118	6/76		10/77	7/117	16/129	0 23	1/42	0/78	17/194	8 1

nosis of malignancy was confirmed by the outcome of the disease and some rare tumours too infrequent to permit a statistical analysis (clear cell or cylindric cell carcinoma, etc) The undifferentiated carcinoma unlike the squamous cell carcinoma, was encountered more often in patients under 50 years of age (43 and 21 per cent, respectively) The patients were classified according to the TNM criteria proposed by the American Joint Committee for Cancer Staging and End Results Reporting (1974)

On admission, 36 6 per cent of the patients had hilar lymph nodes (N1), 60 3 mediastinal involvement (N2) and 33 5 per cent had distant metastases [illegible]

[illegible] carcinomas (56 8 %) but almost the same incidence of distant metastases (33 and 29 3 per cent, respectively) The group with unspecified

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Malignant lung tumours are still a challenge for the therapist, particularly because the diagnosis is often made at a very late stage Generally, the patients referred for radiation therapy are too advanced for surgery, but hope should not be abandoned as a fair chance remains of palliation with chemotherapy The results of radiation therapy in this heterogeneous group of patients are poor but many long term survivals have been reported in the literature and many authors defend the usefulness of irradiation (BLOEDORN et coll 1962, HUSTU & NICKSON 1964, DEELEY 1973, MOSS and coll 1973) *The experience at this unit is presented in this report*

Material

During the period from 1967 to 1971, 194 patients with malignant lung tumours were irradiated The sex and age distribution agreed with published data (Table 1) 176 males and 18 females (ratio 10 1) with the highest incidence between 51 and 60 years

The microscopic diagnosis was of squamous cell carcinoma in 29 8 per cent, undifferentiated 'oat cell carcinoma in 26 2, adenocarcinomas in 2 5 and unspecified malignant tumours in 41 2 per cent *This latter group included all cases with malignant* cytology but without well defined histology, very advanced cases in which the diag-

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Table 1

Malignant lung tumours in 194 patients Distribution by microscopy, age and sex

Microscopy	30 years		31–40		41–50		51–60		61–70		71		Total			
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	No of cases	Per cent
Squamous cell carcinoma			5	3	13	1	27		8		1		54	4	58	29 8
Adenocarcinoma					2		2	1					4	1	5	
Undifferentiated carcinoma	2		10	2	7	1	18		9	1	1		47	4	51	26 2
Other types			2	2	15	2	23	4	23	1	8		71	9	80	41 2
Total	2		17	7	37	4	70	5	40	2	10		176	18	194	

Table 2

Malignant lung tumours in 194 patients The 3 year survival in relation to the TNM staging

Microscopy	Tumour			Regional lymph nodes			Distant metastases			Fever	Total	
	1	2	3	0	1	2	0	1	2		No of cases	Per cent
Squamous cell carcinoma	—	4 43	1 15	—	4/25	1/33	5 41	0 7	0 10	0 19	5/58	8 6
Adenocarcinoma	—	1/3	0 2	—	1/4	0 1	1 2	—	0 3	0 1	1 5	20
Undifferentiated carcinoma	—	2/20	0 31	—	0 13	2 38	2/34	0 9	0 8	0 27	2/51	3 9
Other types	—	4 52	5/28	—	5/35	4/45	8 52	0 7	1/21	0 31	9 80	11 2
Total		11/118	6/76		10 77	7/117	16 129	0 23	1 42	0 78	17 194	8 1

nosis of malignancy was confirmed by the outcome of the disease and some rare tumours too infrequent to permit a statistical analysis (clear cell or cylindric cell carcinoma, etc) The undifferentiated carcinoma unlike the squamous cell carcinoma, was encountered more often in patients under 50 years of age (43 and 21 per cent, respectively) The patients were classified according to the TNM criteria proposed by the American Joint Committee for Cancer Staging and End Results Reporting (1974)

On admission, 36 6 per cent of the patients had hilar lymph nodes (N1), 60 3 mediastinal involvement (N2) and 33 5 per cent had distant metastases 11 8 per cent supraclavicular lymph nodes (M1) and 21 6 per cent in other sites (M2, Table 2) The undifferentiated carcinomas had a greater involvement of mediastinal lymph nodes (74 5 %) than the squamous cell carcinomas (56 8 %) but almost the same incidence of distant metastases (33 and 29 3 per cent, respectively) The group with unspecified

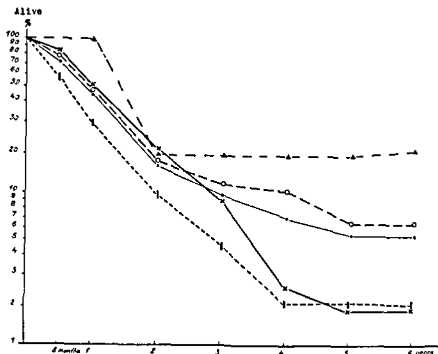


Fig 1 Survival curves after telecobalt therapy alone, in relation to microscopy in 154 patients The 3- and 5-year survival figures for all cases were 9 7 and 5 4 %, respectively, 9 and 2 % for squamous cell carcinoma and 4 6 and 2 3 % for undifferentiated carcinoma ▲— —▲ Adenocarcinoma ×—× Squamous cell carcinoma |--| Undifferentiated carcinoma ○—○ Other types ●—○ All cases

microscopy included a great number with mediastinal lymph nodes (56 %) and distant metastases (35 %) Fever was recorded in 40 2 per cent of the cases and was most often associated with the undifferentiated carcinoma (52 9 %) All the patients belonged to stages II or III, which may explain the poor results of the radiation therapy

Technique The treatment was carried out with telecobalt, the patients being irradiated through antero-posterior opposed fields with a basic dose of 4 000 rad over 4 weeks in 20 fractions to the primary tumour and the whole mediastinum The patients who had radical treatment received a boost of 2 000 rad with an oblique beam corrected for lung transmission to the primary tumour and the adjacent mediastinum The final dose was 6 000 rad for radical treatment and 4 000 rad for palliation For patients in poor general condition split-course irradiation was used Chemotherapy was introduced only if the disease progressed after radiation therapy

Results

The length of survival calculated from the first day of irradiation for the whole group of 194 patients was 8 1 per cent (17/194) at 3 years and 7 per cent (7/99) at 5 years but these percentages alone are of little value for an appreciation of the

Table 3

Squamous cell carcinoma of the lung in 58 patients The 3 year survival in relation to the T and N categories

	Tumour			Total
	1	2	3	
N0	—	—	—	—
N1	—	3/20	1/5	4 25
N2	—	1/23	0 10	1/33
Total	—	4 43	1/15	5 58

usefulness of radiation therapy Of these patients, 34 were treated only for distant metastases, 2 died during the treatment and 4 were irradiated postoperatively (with 2 survivals over 5 years) The remaining 154 patients were treated by irradiation of the primary tumour alone with a survival of 9 7 per cent (15/154) at 3 years and 5 4 (5/92) at 5 years Particularly in the first two years the mortality is high irrespective of the histologic type (Fig 1) and the survival curves have a tendency to become parallel and equal, a fact explained by the few number of survivors in each category The undifferentiated carcinoma has the worst prognosis 56 per cent survivals at 6 months, 28, 9 3 and 4 6 per cent at 1, 2 and 3 years respectively, as compared with the squamous cell carcinoma 79, 47 6, 20 4 and 9 per cent survivals at the same time intervals

The analysis of survival related to the TNM criteria emphasizes the prognostic significance of these parameters (Table 2) as well as the stage of the disease at the beginning of irradiation The duration of survival is closely correlated to the extent of the disease (Table 3) one survival at 3 years in the stage N2 or T3

Apart from microscopy and the TNM categories there was another parameter with prognostic significance a fever over 38°C persisting during the course of irradiation despite antibiotic treatment No patient in this category lived more than one year whatever the microscopy or the TNM staging

The mean survival was 15 months for all cases, with 13 6 months for squamous cell carcinoma and 9 3 months for undifferentiated carcinoma Even if these figures are modest, the results of telecobalt therapy on the quality of life may be said to be good since almost half the patients were able to lead an active life for at least one year with relief of all or a great part of their symptoms (pain, hemoptysis, respiratory deficiency, etc)

Complications were few The most frequent was an irradiation oesophagitis at 3 000 rad which could be managed easily with symptomatic treatment and a semi-fluid diet Two patients died during the radiation therapy due to a massive pulmonary hemorrhage at a dose of 3 200 and 1 300 rad respectively The therapeutic failures were dominated by the development of distant metastases In 114 patients the cause

Table 4

Malignant lung tumours Cause of death in 114 patients

Microscopy	Primary tumour	Tumour + metastases	Metastases
Squamous cell carcinoma	12	1	15
Adenocarcinoma			2
Undifferentiated carcinoma	13	2	18
Other types	*16*	7	28
Total	41	10	63
Per cent	35 9	8 7	55 2

of death could be established and was due to the primary tumour in 35 9 per cent, to distant metastases in 55 2 and to both the primary tumour and metastases in 8 7 per cent (Table 4)

Discussion

The prognosis in malignant lung tumours is related to the microscopic type and to the extension of the disease The clinical TNM staging is simple and reliable and is of value in estimating the prognosis and in determining the appropriate therapy In addition, some clinical signs, such as fever or weight loss, may indicate a poor prognosis, as in the malignant lymphomas However, the efficacy of the radiation therapy is also influenced by the irradiation technique the volume irradiated, the field shape and the individual radiation tolerance

The material has been divided into 5 groups according to the extension of the disease and the treatment used

A Small hilar, parahilar or apical tumours (T1 – 2, N0 – 1 – 2, M0) which can be included in an area less than 150 cm² (64 patients)

B Large hilar and parahilar tumours, or tumours of the lower lobes, which are included in an area more than 150 cm² with irregular fields, as well as peripheral lesions with hilar lymph nodes (T1 3, N1 2, M0) (24 patients)

C Undifferentiated carcinomas (43 patients), which due to the rapid growth and early onset of metastases have a bad prognosis in spite of the good local response to irradiation The superior vena cava syndrome is included in this group also since the irradiation technique is similar

D Postoperative irradiation (4 patients)

E Palliative treatment (59 patients) In the presence of distant metastases or a poor general condition, the only aim was to improve the quality of life

The analysis of survival in each of these groups indicates the practical usefulness of this division Group A had the best prognosis with 65 7, 29 7, 12 3 and 7 6 per cent at 1, 2, 3 and 5 years, respectively, against 37 5, 12 5, 8 3 and 4 3 per cent for

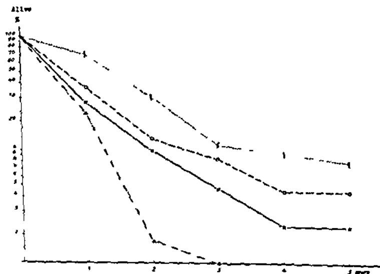


Fig 2 Survival c... were 12 5 and 7 ... 8 5 and 4 3 % for ... (group C) Ther... A (64 patients) ... Group E (59 patients)

group B (Fig 2) No patient from group E lived more than 3 years These figures indicate the relationship between the irradiated volume and the likelihood of irradiation slowing the growth and spread of the disease Patients belonging to group A can be treated by irradiation alone In all other cases irradiation alone does not give satisfactory results and in the future chemotherapy will be given in addition to the irradiation in the hope of improving the clinical results Because the appearance of metastases was the main cause of failure, an attempt was made to stimulate the immunologic response Based on some experimental results (KIRICUTA et coll 1973) nonspecific imm... bined with Hep... in 1973 The or... ficant due to t... of patients 53 3 per cent (8/15) for group A, 31 5 per cent (6/19) for group B and for groups C and E 1/6 and 1/14, respectively This trial is continuing

Conclusions The prognosis of malignant lung tumours is related to the microscopic appearance and to the extent of the disease Except for the undifferentiated carcinoma which eludes classification due to its rapid development, the TNM staging is a useful and reliable aid for evaluating the prognosis and for determining the treatment Poor results of radiation therapy are mainly the consequence of a late stage at the start of irradiation, but it is still possible to achieve much symptomatic improvement

and even some long term survivors Beside microscopy and TNM extent, the results of radiation therapy are related to the size and shape of the volume to be irradiated The central and apical tumours which can be irradiated through a field less than 150 cm², are the only lung tumours which benefit from radical irradiation, with 3 and 5 year survivals of 12 3 and 7 6 per cent, respectively The remaining cases have a worse prognosis due to the onset of metastases which suggests the need for chemo therapy or immunotherapy in addition to radiation therapy to improve the results

SUMMARY

The authors present the results of telecobalt therapy in 194 patients with malignant lung tumours treated between 1967 and 1971 The 3- and 5 year survivals were 9 7 and 5 4% respectively, with an average survival of 15 months The results obtained depend on the microscopy, the clinical staging and on the irradiation techniques possible, several prog nostic groups may be distinguished

ZUSAMMENFASSUNG

Die Verfasser geben die Resultate der Telekobalttherapie von 194 Patienten mit malignen Lungenkarzinomen die während 1967 bis 1971 behandelt wurden Die 3 und 5 Jahres Überlebensrate betrug 9,7% bzw 5 4% mit einer mittleren *Überlebenszeit von 15 Monaten* Die erhaltenen Ergebnisse sind abhangig von dem mikroskopischen Bild dem klinischen Stadium und der moglichen Bestrahlungstechnik Verschiedene prognostische Gruppen *konnen abgegrenzt werden*

RÉSUMÉ

Les auteurs présentent les résultats de la télécobalthérapie chez 194 malades atteints de tumeur maligne du poumon traités entre 1967 et 1971 Les taux de survie à 3 et 5 ans sont respectivement de 9 7 et 5 4 pour cent avec une survie moyenne de 15 mois Les résultats obtenus dépendent de l aspect microscopique du stade clinique et des techniques d irradia tion possibles, on peut distinguer plusieurs groupes de pronostic

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FROM THE DEPARTMENT OF RADIOLOGY, RADIATION CENTER, UNIVERSITY OF LOUISVILLE, LOUISVILLE, KENTUCKY 40201, USA

EFFECT OF CHEMICAL PROTECTORS ON THE RESPONSE OF THE INTESTINE TO ROENTGEN OR FISSION NEUTRON IRRADIATION

C P SIGDESTAD, A M CONNOR and R M SCOTT

Improvement in the therapeutic index in radiation therapy requires a *differential* effect between normal and malignant cells Methods to obtain this differential response are presently under active investigation Recently, newly synthesized phosphorothioate radiation protectors have shown promise in the improvement of the therapeutic index in animals (YUHAS & STORER 1969, LOWY & BAKER 1973, HARRIS & PHILLIPS 1971, PHILLIPS et coll 1973, and others) It has been proposed that the differential effect obtained with compounds of this type was due to poor tumor vascularity, hence little protector was delivered to the tumor (YUHAS & STORER) In addition, the tumor may have had a high proportion of hypoxic cells which have been shown to be protected less than well oxygenated cells (HARRIS & PHILLIPS)

In a series of experiments various phosphorothioates and conventional protectors were tested for their ability to modify the effects of roentgen of fission neutron irradiation S 2 (3 amino propylamino)ethylphorothioic acid (WR-2721) was found to be an exceptionally good protector against either roentgen radiation (SIGDESTAD et coll 1975a) or fission neutrons (SIGDESTAD et coll 1976) Dose modification factors (DMF) of 1 6 were found for either modality in crypt survival investigations

Mercaptoethylamine (MEA) and its phosphorothioate derivative (WR-638) were

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and even some long term survivors Beside microscopy and TNM extent, the results of radiation therapy are related to the size and shape of the volume to be irradiated The central and apical tumours which can be irradiated through a field less than 150 cm², are the only lung tumours which benefit from radical irradiation, with 3 and 5 year survivals of 12 3 and 7 6 per cent, respectively The remaining cases have a worse prognosis due to the onset of metastases which suggests the need for chemotherapy or immunotherapy in addition to radiation therapy to improve the results

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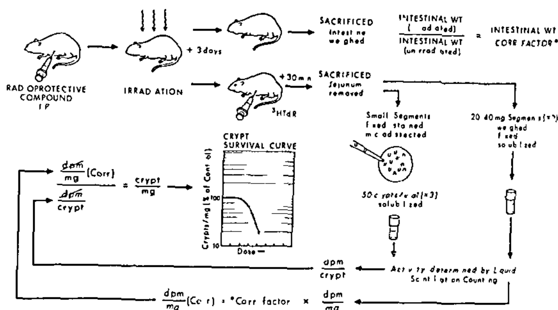


Fig 1 Schematic drawing of the intestinal crypt survival method

also tested (SIGDESTAD et coll 1975b) and found to be good protectors, but less effective than WR-2721.

The present report compares another phosphorothioate, S-1-(2-hydroxy-3-amino) propylphosphorothioic acid (WR-77913) and AET for their ability to protect the intestinal cell renewal system from roentgen or fission neutron irradiation

Material and Methods

The animals used were male, C57/Bl 6-J mice They were approximately 100 days of age and were kept in environmentally controlled rooms and fed standard mouse pellets and water ad libitum

Protectors WR-77913 is the monosodium salt of S-1-(2-hydroxy-3-amino) propylphosphorothioic acid and was obtained from the Medicinal Chemistry Division of the Walter Reed Institute of Research The toxic LD_{50} was tested and found to be 1 224 (1 119–1 320) mg/kg Approximately two thirds of the toxic LD_{50} were used (820 mg/kg) throughout this investigation No drug-related deaths occurred with this dosage

AET (S 2-amino ethylisothiuronium Br HBr) was purchased commercially The toxic LD_{50} was found to be 295 (280–310) mg/kg

Both WR-77913 and AET were dissolved in water and injected intraperitoneally 15 to 30 min before irradiation Logistics of reactor operation precluded more precise timing of the injection to irradiation time

Table

Salient data on intestinal crypt survival and lethality in mice irradiated with roentgen rays or fission neutrons with or without chemical protection

Treatment	D_0	n	D_q	GI*	$LD_{50(6)}$	95% CL	DMF	GI**
Roentgen rays only	395	6 1	716	—	1 277	1 194 1 376	1 0	—
Roentgen rays + AET	435	14 3	1 158	488	1 813	1 715-1 909	1 42	536
Roentgen rays + WR 77913	818	3 1	938	515	1 812	1 701 1 984	1 42	535
Neutrons only	95	5 2	156	—	252	222 298	—	—
Neutrons + AET	157	3 2	181	69	302	89 341	1 20	50
Neutrons + WR 77913	136	5 4	229	102	372	340-412	1 48	120

* Gy increase at 50% crypt survival

** Gy increase at $LD_{50(6)}$ (protected $LD_{50(6)}$ — unprotected $LD_{50(6)}$)

Roentgen irradiation The procedures were carried out with a 4 MeV linear accelerator (Varian Clinac-4) The mice were irradiated unrestrained in a lucite container 30 cm in diameter and 4 cm high The container was rotated 3 rpm in a 32 cm × 32 cm field which was known to be extremely flat with regard to dose variation The source-skin distance was 80 cm with a dose rate of 2 5 Gy/min (250 rad/min)

Dosimetry was accomplished with a Victoreen ionization chamber at equilibrium depth in a polystyrene calibration block with appropriate corrections

Neutron irradiation The Health Physics Research Reactor (Dosar), Oak Ridge National Laboratory, was used for neutron irradiation The reactor facility has been described in some detail (AUXIER 1965) The fission spectrum had a peak energy of 0 9 MeV and a mean energy of 1 2 MeV The mice were irradiated in nylon tubes 2 m from the unshielded core The power level was 6 kW with a dose rate of about 0 55 Gy/min Gamma contamination amounted to about 14 per cent of the dose A good discussion of dose and LET distribution in small animals using this reactor was presented by WILLHOIT & JONES (1970) SIGDESTAD et coll (1972) have previously described the RBE for this irradiation procedure

Lethality Groups of mice were injected with either WR-77913, AET or water 15 to 30 min before irradiation Whole body doses ranged from 1 8 to 5 Gy for neutron irradiation and from 9 to 22 Gy for roentgen irradiation The $LD_{50(6)}$ was calculated by probit analysis method of FINNEY (1963) The dose modification factor (DMF) was calculated as a ratio of protected to unprotected $LD_{50(6)}$ values

Crypt assay procedure Intestinal crypt survival, i e crypts per milligram wet weight jejunum was measured 3 days after irradiation A schematic drawing of the assay procedure appears in Fig 1 Details of the procedure have been presented previously (HAGEMANN et coll 1971) Briefly, crypts per milligram intestine are

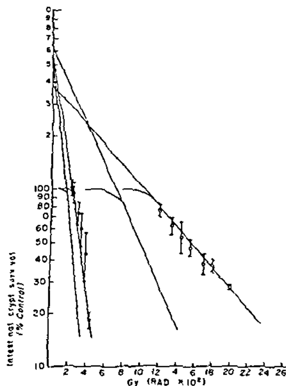


Fig 2

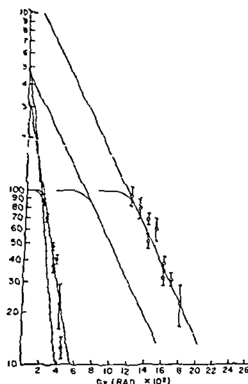


Fig 3

Fig 2 Crypt survival curves for WR 77913 treated mice irradiated with either 4 MeV roentgen rays or fission neutrons Lines without data points represent unprotected but irradiated controls

Fig 3 Crypt survival curves for AET treated mice irradiated with either 4 MeV roentgen rays or fission neutrons Lines without data points represent unprotected but irradiated controls

determined by the ratio of dpm/mg intestine and dpm/crypt 30 min after injection of ³HTdR The crypts/mg intestine determined in groups of mice given various doses of roentgen or neutron radiation are compared to unirradiated controls A semi log plot of crypt/mg in per cent of control versus dose described the crypt survival curve

Total and per crypt cellularity Previously reported data (HAGEMANN et coll, HAGEMANN & LESHER 1971) indicate that while dpm/mg and dpm/crypt differ from unirradiated controls at 3 days after irradiation, the dpm/labeled nucleus does not These results demonstrate that the dpm/mg and dpm/crypt values are good indicators for the total and per crypt DNA-synthesizing cell population This, in turn, is a reflection of the size of the proliferative compartment

Results

Lethality Unprotected mice exposed to 4 MeV roentgen radiation were found to have an $LD_{50(6)}$ value (Table) of 12 77 (11 94–13 76) Gy Mice protected with WR-77913 or AET had $LD_{50(6)}$ values of 18 12 Gy and 18 13 Gy, respectively This resulted in a DMF value of 1 42 for each protector The so-called Gy increase (GI) values (YUHAS 1971) were *5 35 and 5 36 Gy, respectively*

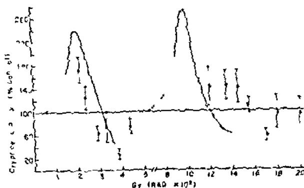


Fig 4 Crypt cellularity as a function of dose in roentgen or neutron irradiated mice protected with WR-77913 The curves without data points represent unprotected but irradiated control

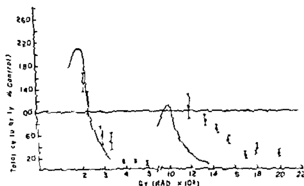


Fig 5 Total cellularity as a function of dose in roentgen or neutron irradiated mice protected with WR 77913 The curves without data points represent unprotected but irradiated control

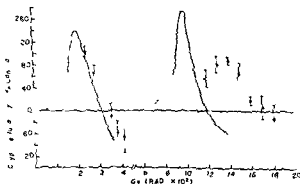


Fig 6 Crypt cellularity as a function of dose in roentgen or neutron irradiated mice protected with AET The curves without data points represent unprotected but irradiated control

Mice irradiated with fission *neutrons without* the benefit of protection had an $LD_{50(6)}$ value of 2 52 (2 22-2 98) Gy *With* WR-77913 the $LD_{50(6)}$ was increased to 3 72 (...) Gy Mice pretreated with AET ... of 1 2

Intestinal crypt ... val is presented in the Table a... points are results

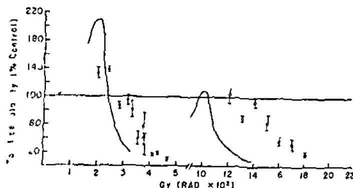


Fig 7 Total cellularity as a function of dose in roentgen or neutron irradiated mice protected with AET The curves without data points represent unprotected but irradiated control

obtained from animals irradiated without benefit of chemical protection Crypt survival curves in mice pretreated with WR-77913 is presented in Fig 2 The slope is significantly different from the *unprotected group irradiated with roentgen rays* This is also seen, but to a lesser extent, in the neutron irradiated group protected *with WR-77913* These results correlate with the probit curves obtained in the lethality experiments inasmuch as linearity but not parallelism was found

Roentgen irradiated mice pretreated with AET (Fig 3) showed a crypt survival curve which was parallel to the unprotected curve The GI for crypt survival (difference between protected and unprotected curves at the 50 per cent crypt survival *level) was 5 15 Gy For unexplained reasons the crypt survival curve for AET pro*tected neutron irradiated mice was not parallel to the unprotected but showed a *slight increase in slope*

Intestinal cellularity The cellular dose response in the crypt 3 days after irradiation has been described previously (SIGDESTAD et coll 1972, 1973, 1975)

The effects of WR-77913 and AET in the cellular response appear in Figs 4 to 7 The curves without data points are results obtained in irradiated but unprotected mice (SIGDESTAD et coll 1975)

It is apparent in these data, as seen in crypt survival, that protection from neutron irradiation is slight with these agents However, when low LET radiation is used protection is seen as a shifting of the cellularity curves to higher doses

Discussion

The continued improvement of irradiation procedures depends upon a difference in effectiveness of radiation on normal and malignant cells This can be accomplished by either radiation sensitizers which preferentially protect sensitized malignant cells or by radiation protectors which preferentially protect normal cells

The phosphorothioate class of chemical protectors are receiving considerable attention for possible use in radiation therapy Primarily this is due to a differential protection of normal cells first reported by YUHAS & STORER These results were confirmed and expanded by HARRIS & PHILLIPS The proposed mechanism of this differential effect is thought to be due to a reduced concentration of the protector in

tumor tissue (YUHAS & STORER) and to a reduction in the oxygen enhancement ratio (HARRIS & PHILLIPS) The differential distribution of labeled WR-2721 was demonstrated by whole body autoradiography by UTLEY et coll (1975) They found that the tumor uptake of the protector was less than normal tissue uptake

Previously the protective effects of WR-2721 against roentgen radiation were reported (SIGDESTAD et coll 1976) Mercaptoethylamine (MEA) and its phosphorothioate derivative (WR-638) were also compared for protective effects (SIGDESTAD et coll 1975b) on the intestinal epithelium Of the compounds tested to date, WR-2721 is the most effective protector against effects of roentgen radiation on the gut with a DMF of 1 64 DMF obtained with other protectors in descending order was WR 638, 1 57, WR-77913, 1 42, AET, 1 42 and MEA, 1 26 When fission neutrons were used the DMF was somewhat reduced, WR-2721, 1 56, WR-77913, 1 48, WR 638, 1 42, MEA, 1 39 and AET, 1 20 It is apparent from these data that the phosphorothioate class of protector is more effective than conventional protectors (MEA and AET)

An interesting and possibly important finding in the present report is the increased slope in the roentgen crypt survival curve in animals pretreated with WR-77913 This slope change may indicate that the drug is affecting oxygen concentration in the crypt cells This finding is substantiated by the probit lethality curves which were linear but not parallel Non parallelism indicates a difference in the mechanism of killing If tissue hypoxia were induced and the distribution of the agent was similar to WR 2721, then the potential use in a clinical situation may be enhanced An additional advantage is that WR 77913 is less toxic (LD_{50} = 1 224 mg/kg) than WR 2721 (LD_{50} = 704 mg/kg)

The data obtained from the cellularity examinations demonstrate the effectiveness of these protectors at the cell level Three distinct phases of compensation occur in the crypt 3 days after irradiation (1) At low doses the crypt begins the compensatory response which is seen with a greater than normal S phase cell content This response is directly related to the dose (2) The peak response where the crypt is maximally stimulated (commensurate with radiation injury) to maintain cell input to the villus (3) The final phase appears at higher doses where the crypt cells are so depopulated that an effective response is not possible In this phase the response is inversely related to the dose, however, it rarely returns to levels less than control These 3 phases are observed subjectively during the crypt dissection procedure

Total intestinal cellularity (dpm/mg in per cent of unirradiated control) responds somewhat differently than crypt cellularity The compensatory response of the entire intestine is due to (1) the effect of irradiation on surviving crypts, i e radiation injury and compensatory response and (2) the inability of some crypts to survive the radiation insult Both effects are responsible for an overshoot somewhat less than observed in the crypts while the loss of entire crypts reduces total S phase cellularity to levels much lower than in the crypt

Acknowledgement

The authors wish to thank Ms Judy Dombrowski and Mrs Pamela Montgomery for expert technical assistance They wish to express their appreciation to the Kentucky Division of the American Cancer Society, and the Honorable Order of Kentucky Colonels for their support The authors are also indebted to the Oak Ridge National Laboratory Dosar staff, especially to Mr W Fox and Mr Donald Ward, for expert reactor operation and dosimetry

SUMMARY

The monosodium salt S-1-(2-hydroxy-3-amino) propylphosphorothioic acid (WR-77913) and S-2-amino ethylisothiuronium Br HBr (AET) were tested for protective effects against 4 MeV roentgen irradiation and fission neutrons in the mouse intestine The parameters tested were intestinal crypt survival, lethality and intestinal crypt cellularity The results showed both compounds to be good protectors in animals The crypt survival curve for roentgen-irradiated mice treated with AET was parallel to that of the untreated group and was displaced to the right by 4 88 Gy (488 rad) Protection from neutron irradiation was less effective with a displacement of only 0 69 Gy (69 rad) Pretreatment with WR-77913 increased the slope of the crypt survival curve in roentgen-irradiated mice This was also seen to a much less extent in neutron-irradiated animals The displacements of the curves (at 50 per cent crypt survival) were found to be 5 15 and 1 02 Gy (515 and 102 rad) for roentgen and neutron irradiation, respectively The lethality experiments showed a dose modification factor (DMF) of 1 42 for both drug-tested groups of roentgen irradiated mice The dose modification factors for fission neutron irradiated mice were 1 48 and 1 2 for WR-77913 and AET-treated mice, respectively The effect of these protectors on crypt cellularity is also discussed

ZUSAMMENFASSUNG

Es wurden das Mononatrium Salz S-1-(2-Hydroxy-3-Amino) Propylphosphorothioic Saure (WR-77913) und S-2-Amino Aethylisothiuronium Br HBr (AET) hinsichtlich ihres Schutzeffektes gegenuber 4 MeV Rontgenstrahlung und Fusionsneutronen am Mausedarm untersucht Die untersuchten Parameter waren das Überleben der Darmkrypten, die Letalitat und die Zellularitat der Darmkrypten Die Ergebnisse zeigen fur beide Substanzen einen guten Schutz bei Tieren Die Überlebenskurve der Krypten der Rontgenbestrahlten und mit AET behandelten Tiere lag parallel zu derjenigen der unbehandelten Tiere und war um 4 88 Gy (488 rad) verschoben Der Schutz gegenuber Neutronenbestrahlung war weniger wirksam mit einer Verschiebung um nur 0,69 Gy (69 rad) Die Vorbehandlung mit WR-77913 hob die Neigung der Überlebenskurve der Krypten bei den Rontgenbestrahlten Mausen Das war auch in geringerem Umfang bei den Neutronenbestrahlten Tieren zu sehen Die Verschiebungen der Kurven (bei 50% Überleben der Krypten) betrug 5,15 und 1,02 Gy (515 und 102 rad) fur Rontgen bzw Neutronebestrahlung Die Letalitatsuntersuchungen zeigten einen Dosis-Modifikations Faktor (DMF) von 1 42 fur beide Testsubstanzen bei den Rontgenbestrahlten Gruppen von Mausen Die Dosis-Modifikations-Faktoren fur die mit Fusionsneutronen bestrahlten Mausen betrugen 1 48 und 1,2 fur die mit WR-77913 bzw AET-behandelten Mause Es wird ebenfalls der Effekt der Schutzsubstanzen auf die Zellularitat der Krypten diskutiert

RÉSUMÉ

Les auteurs ont testé sur l intestin de la souris l effet protecteur contre l irradiation par des rayons roentgen de 4 MeV et contre les neutrons de fission le sel monosodé de l acide S-1-(2-hydroxy-3 amino) propylphosphorothioique (WR-77913) et du S-2 amino éthyliso thiuronium Br HBr (AET) Les paramètres testés ont été la survie des cryptes intestinales, la léthalité et la cellularité des cryptes intestinales Les résultats ont montré que ces deux

corps sont de bons protecteurs chez les animaux La courbe de survie des cryptes pour les souris irradiees par les rayons roentgen et traitées avec AET a été parallèle à celle du groupe non traité et est déplacée vers la droite de 4 88 Gy (488 rad) La protection contre l irradiation par les neutrons a été moins efficace avec un deplacement de 0 69 Gy (69 rad) Le traitement préalable par le WR-77913 augmente la pente de la courbe de survie des cryptes chez les souris irradiées par les rayons roentgen Cet effet est constaté aussi, dans une beaucoup moins grande mesure, chez les animaux irradiés par les neutrons Les déplacements des courbes (pour une survie des cryptes de 50 %) sont de 5,15 et 1,02 Gy (515 et 102 rad) respectivement pour les rayons de roentgen et pour les neutrons Les expériences sur la lethalite ont montre un facteur de modification de doses (DMF) de 1,42 pour les deux groupes de souris irradiées par les rayons roentgen traitées par ces 2 agents Les facteurs de modification de doses pour les souris irradiées par les neutrons de fission sont 1,48 et 1,2 respectivement pour les souris traitées par le WR 77913 et par AET Les auteurs examinent aussi l effet de ces protecteurs sur la cellularite des cryptes

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available kit (batch No L 805/74 and 515/75 EHDP, AB Atomenergi, Studsvik, Sweden) Each vial contained 5 mg EHDP and 100 μg $SnCl_2$ Carrier-free $^{99}Tc^m$-pertechnetate was obtained as a NaCl-eluate from a $^{99}Mo/^{99}Tc^m$ generator (Philips-Duphar) Each animal was given a dose of 1 0 mCi in 0 3 to 0 5 mg of EHDP

Experimental procedure Six 8 day-old rats and seven 12-day-old rats of the Sprague-Dawley strain were used The younger animals had a mean weight of 19 g, the older of 27 g Each animal was injected intraperitoneally with 0 3 to 0 5 ml of the solution The animals were killed as follows 5 after 30 minutes, 2 after 3 hours, 5 after 6 hours and 1 animal after 9 hours

At the selected time, the animals were anaesthetized with ether and then mounted on microtome stages, which contained carboxymethyl cellulose mixed with water to a semiliquid consistency The stage was immersed in a mixture of hexane and solid CO_2 (−75°C)

In a freeze-box (−15°C), 20 μm thick sagittal sections were cut at different levels through the whole animal The sections and films were then treated according to a method previously described (ULLBERG 1954, ROHLIN & HAMMARSTRÖM 1976)

Results

The distribution of $^{99}Tc^m$ labelled EHDP was characterized by a rapid and high uptake of the isotope in bone and dentine, a rapid but moderate one in the urinary system and a slow uptake in the liver and spleen

The highest concentrations of the isotope were found in the growing surfaces of bone and dentine already 30 minutes after injection (Figs 1 a, 2 a) In contrast, developing enamel had a low concentration of the isotope (Fig 2 a) The concentration in the circulating blood was rather low, although higher than in other soft tissues, except for the tissues close to the injection site and those of the urinary system

The distribution of the isotope 3, 6 and 9 hours after injection was similar to that observed after 30 minutes, with an uptake predominantly in bone and dentine

After 3 hours, soft tissue uptake of isotope was located mainly to the urinary system (Fig 1 b) The concentration was high in the pelvis of the kidney, the ureters and the urinary bladder In addition, there was a moderate accumulation of the isotope in the renal cortex

In the enamel, the concentration after 6 hours was higher than after 30 min (Fig 2) No difference in uptake could be observed between 6 and 9 hours An additional uptake of activity was observed in the liver and spleen 6 and 9 hours after injection (Figs 1 c d) The distribution within those organs was uneven In the liver the isotope was found in small spots and in the spleen the highest concentrations were found at the border between the red and white pulp with a somewhat lower concentration found in the red pulp The concentrations in the liver, spleen and kidney were about the same after 6 and 9 hours

FROM THE DEPARTMENTS OF ORAL ROENTGENOLOGY (DIRECTOR: PROF K.-Å. OMNELL) AND ORAL HISTOPATHOLOGY (DIRECTOR: PROF L. HAMMARSTRÖM), UNIVERSITY OF LUND, S-214 21 MALMÖ, SWEDEN

WHOLE-BODY AUTORADIOGRAPHY OF $^{99}Tc^{m}$-LABELLED ETHYLENE-1-HYDROXY-1, 1-DIPHOSPHONATE (EHDP) IN YOUNG RATS

MADELEINE ROHLIN

Since the introduction of $^{99}Tc^{m}$-labelled polyphosphate (SUBRAMANIAN & MCAFEE 1971) several other $^{99}Tc^{m}$-labelled compounds have been used for skeletal imaging. Thus, $^{99}Tc^{m}$ has been combined with pyrophosphate and diphosphonates such as *ethylene-hydroxydiphosphonate*, *methylene-diphosphonate* and *amino-etyhl-diphosphonate* (SUBRAMANIAN et coll. 1974). Most reports and comparisons of $^{99}Tc^{m}$-labelled compounds (DUNSON et coll. 1973, SUBRAMANIAN et coll. 1974 and BÜLL et coll. 1974) have been based on examination of samples from particular organs and tissues such as blood, urine, kidneys, liver, muscles and skeleton. In the present investigation, the distribution of $^{99}Tc^{m}$-labelled ethylene-1-hydroxy-1, 1-diphosphonate was analysed using whole-body autoradiography. This method gives a general view of the distribution of the injected isotope in all the tissues of the body. It also depicts the uptake in a clearer way than well-counting techniques and has a better resolution than scintigraphy.

Material and Methods

Labelled compound. $^{99}Tc^{m}$-labelled ethylene-1-hydroxy-1, 1-diphosphonate (EHDP) was prepared by adding 5 ml carrier-free $^{99}Tc^{m}$-pertechnetate to a commercially

Submitted for publication 30 April 1976

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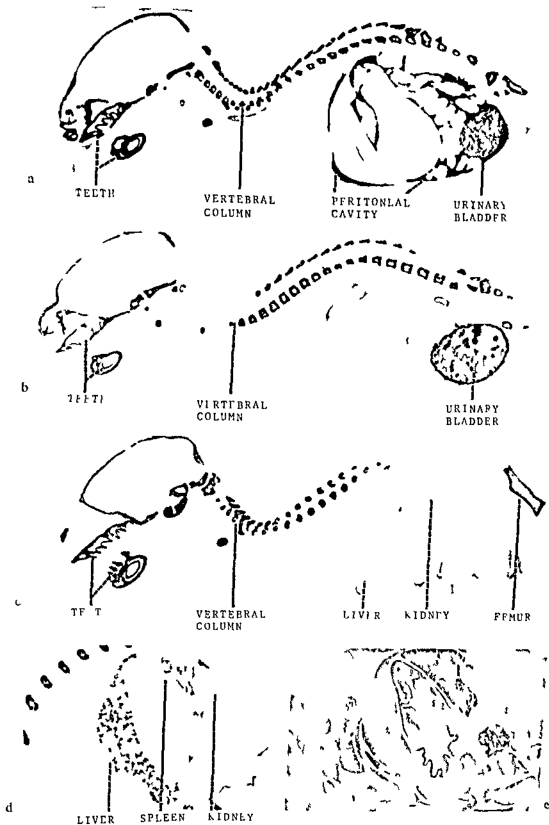


Fig 1 (For legend see opposite page)

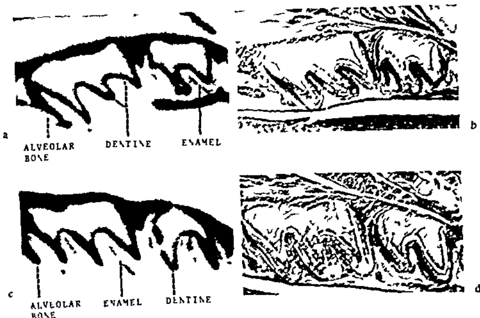


Fig 2 Autoradiograms of the upper jaw (a c) after i p injection of ^{99}Tc^{m} labelled EHDP with the corresponding sections (b d) a) 30 min and c) 6 hours after injection High uptake (black) in the dentine of the developing molars and in the alveolar bone In the tooth enamel slight uptake somewhat higher after 6 h than after 30 min

Discussion

The accumulation of ^{99}Tc^{m} in bone was very rapid after an injection of ^{99}Tc^{m}-labelled EHDP, as was the clearance from blood and other soft tissues except for the urinary system This is in agreement with several other reports, for example that of SUBRAMANIAN et coll (1972), in which samples from major organs were assayed for activity in a scintillation well-counter, and that of CALLAHAN & CASTRONOVO (1973) in which scintiphotos were obtained from rabbits at various time intervals after an intravenous injection The present method is mainly a qualitative one, thus yielding good information concerning the distribution of the isotope The distribution of ^{99}Tc^{m} labelled EHDP and ^{99}Tc^{m} labelled pyrophosphate seemed to be identical and very similar to those of the bone seeking substances ^{85}Sr-chloride and ^{32}P labelled pyrophosphate (ROHLIN & HAMMARSTROM) Most authors (CITRIN 1974 DUNSON et coll HOSAIN et coll 1973, SUBRAMANIAN et coll 1974) considered ^{99}Tc^{m} labelled

Fig 1 Autoradiograms from 8-day old rats af
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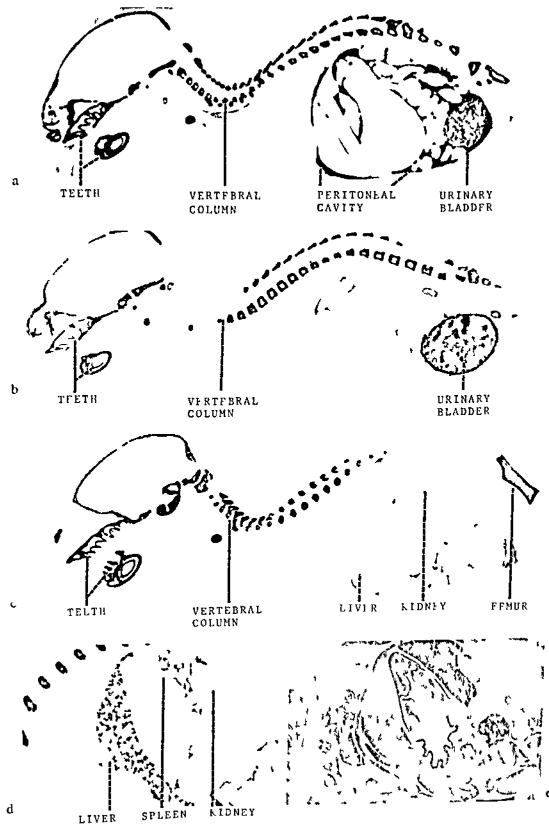


Fig 1 (For legend see opposite page.)

results of the present experiments rather suggested the in vivo formation of a colloid. The late uptake in the liver and spleen might indicate a metabolic pathway for that part of the substance which was initially accumulated in the skeleton

The autoradiograms indicated that most of the substance was excreted via the urine That part of the elimination of $^{99}Tc^{m}$-labelled EHDP seemed to be similar to $^{99}Tc^{m}$ labelled pyrophosphate but unlike $^{99}Tc^{m}$ pertechnetate, which was eliminated both via the faeces and the urine (ROHLIN & HAMMARSTRÖM)

Acknowledgement

Thanks to Prof Bertil Nosslin, Department of Nuclear Medicine, Malmo Allmänna Sjukhus, Malmo, for stimulating discussions and valuable criticism

SUMMARY

The distribution of $^{99}Tc^{m}$ after intraperitoneal injection of $^{99}Tc^{m}$-labelled ethylene-1-hydroxy-1, 1-diphosphonate (EHDP) in young albino rats was investigated by whole-body autoradiography The distribution was characterized by a rapid and high uptake in bone and dentine, a rapid but moderate uptake in the urinary system and a slow and slight uptake in liver and spleen

ZUSAMMENFASSUNG

Die Verteilung von $^{99}Tc^{m}$ nach intraperitonealer Injektion von $^{99}Tc^{m}$-gezeichnetem Äthylen-1-hydroxy-1, 1-Diphosphonat (EHDP) in jungen Albinoratten wurde mittels Ganzkorperautoradiographie untersucht Eine schnelle und hohe Aufnahme im Skelett und Dentin, schnelle aber massige in den Harnwegen und eine langsame und geringe in Leber und Milz charakterisierten die Verteilung

RÉSUMÉ

La distribution du $^{99}Tc^{m}$ apres injection intraperitonéale d ethylene-1-hydroxy-1, 1-diphosphonate marque au $^{99}Tc^{m}$ (EHDP) à de jeunes rats albinos a été étudiée par autoradiographie totale du corps Cette distribution est caractérisée par une fixation rapide et élevee dans l os et dans la dentine, une fixation rapide mais moderee dans le système urinaire et une fixation lente et faible dans le foie et la rate

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EHDP to be superior to pyrophosphate as a bone-seeking compound A more rapid clearance from soft tissues and a higher percentage of urinary clearance occurred when using $^{99}Tc^m$-labelled EHDP However, according to ECKELMAN et coll (1974), the two compounds appeared to be comparable BULL et coll considered $^{99}Tc^m$-labelled pyrophosphate to be the best of these two bone-seeking compounds ECKELMAN et coll emphasized that the total amount of injected phosphate affected the tissue distribution In the present experiments, the dose of phosphate as well as the amount of activity injected were kept constant

The uptake in dentine was similar to that in bone This is to be expected since bone and dentine possess many similarities in formation and structure The uptake of the compound in the enamel region was very low and rather diffuse, which made exact localization difficult Since $^{99}Tc^m$-labelled EHDP in other respects was similar to other bone-seeking isotopes, this uptake is probably localized to the mineralized tissues and not to the ameloblasts or stratum intermedium However, the distribution in the enamel region did not resemble that of $^{45}CaCl_2$ (BERGMAN & HAMMARSTRÖM 1969) Even though the ages of the experimental animals (8- to 12-day-old) were chosen to include different stages of enamel development, there seemed to be no difference in degree of uptake along the cusps The autoradiograms seemed to show an increase of uptake with time, which may indicate that the substance has to be metabolized before it is taken up

The uptake in the liver and spleen appeared to be higher after 6 and 9 hours than after a considerably shorter time SUBRAMANIAN et coll (1972) and TOFE & FRANCIS (1974) found the uptake of $^{99}Tc^m$ in the liver to be higher 24 hours after injection than after 4 hours ECKELMAN et coll recorded increased activity in the liver with increasing pyrophosphate or diphosphonate dose The present phosphate dose was 3 to 10 times higher than that used by ECKELMAN et coll However, the observed increase of activity was time-dependant and probably not due to the high phosphate dose, which was kept constant

The nature of the $^{99}Tc^m$-labelled uptake in liver and spleen is not yet known Apparently, it does not represent free pertechnetate, since this substance did not accumulate in the liver and spleen but was excreted in the gastric mucosa (ROHLIN & HAMMARSTRÖM, among others) The fact that the uptake was located to spots in the liver and the marginal sinuses of the spleen, may suggest the presence of a colloid substance accumulating in the reticuloendothelial cells A colloid, which was prepared from a technetium-tin complex has been used for investigations of the liver (LIN & WINCHELL 1972)

The facts that no activity accumulated in the liver and spleen 30 min and 3 hours after injection and no activity in the thyroid, salivary glands, stomach and intestines during the whole observation time, indicated a high quality of the prepared solution If colloidal particles had existed as preformed components in the solution, the uptake would be very rapid $^{99}Tc^m$-labelled sulphur-colloid was cleared from the blood to 98 per cent within 6 min in rats weighing about 370 g (HANEY et coll 1971) The

FROM THE RESEARCH INSTITUTE OF NATIONAL DEFENCE, S-172 04 SUNDBYBERG, SWEDEN

INFLUENCE OF STEROID HORMONES ON THE CARCINOGENICITY OF ^{90}Sr

A NILSSON and AGNETA BROOMÉ KARLSSON

When oestradiol (Estradurin) was given to mice in combination with ^{90}Sr a highly increased mortality rate was obtained as compared with either treatment alone (NILSSON & RÖNNBACK 1973) The reduction of the mean survival times depended upon early developing blood dyscrasias and a significantly enhanced bone tumour rate concomitant with a substantial reduction of the tumour latency time It was anticipated—since carcinogenesis requires cells capable of proliferation—that factors such as oestrogenic hormones which stimulate the bone cell lines and their precursors to proliferation, may be one of the reasons why these hormones act as promoting events and increase the carcinogenicity of ^{90}Sr in mice Oestrogenic hormones also have a lymphocytolytic effect (DOUGHERTY 1952, DOUGHERTY et coll 1964, KAPPAS & PALMER 1963, THOMPSON et coll 1965) and so have glucocorticosteroids (SELYE 1936, LUNDIN & JÄRPLID 1973) Contrary to oestrogens, these hormones have a general depressing and inhibiting effect of the proliferative capacity of mesenchymal tissues such as the bone cells (NICOLAYSEN 1960, URIST et coll 1963) Anabolic steroids are considered to have a protective effect against destructive factors on the skeleton (BASSETT et coll 1960) The aim of this experiment was therefore to compare the effect of these hormones with that of oestrogens particularly with consideration to factors such as tumour frequency, induction time, life span, tumour types etc

Material and Methods

The experimental procedures are recorded in Table I ^{90}Sr was given intraperitoneally to all mice as $^{90}Sr(NO_3)_2$ Survival times and tumour induction times are

The investigation was carried out as part of the programme of the European Late Effects Project Group (EULEP) Submitted for publication 29 March 1976

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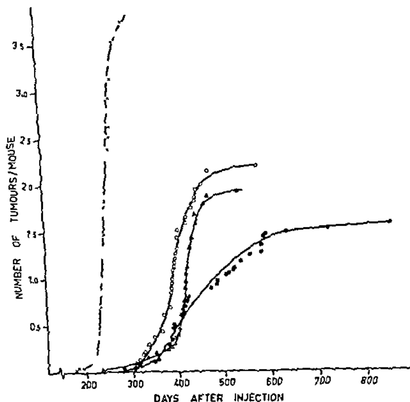
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Between 30 and 53 *overt*, *paraosteal* bone tumours were examined from each of the groups A to D and were classified *according to the* nomenclature recommended by the Committee of Pathology of the European Late Effects Project Group (EULEP, 1971)

Results

Survival time The mean survival times of the four different groups are presented in Table 2 Comparing *with group* A the life span of the C group is reduced with 131 days ($t = 7\,295$, $p > 0\,001$) or 36 4 per cent Group D, on the other hand, survives group A with 93 days ($t = 3\,471$, $p < 0\,001$) or 25 8 per cent, whereas no difference exists between group A and B In *group* A the first mouse died after 161 days in group B after 182 days and in *group D after 200* days In group C 4 mice were dead before day 50

Frequency of bone tumours In Table 2 the frequency of tumour bearing mice, total number of tumours and number of tumours per mouse are recorded In Fig 1 the

Table 1

Experimental design Day 0 Start of experiment All mice 75 ± 3 days old CBA females Oestrogen (polyoestradiolphosphate) was given as Estradurin, anabolic steroid (nortestosterone) as Deca Durabol and glucocorticosteroid (methylepredmsolone) as Depomedrone

Group of mice	No of mice	Day 0 Hormone mg s c	Day 7 kBq (μCi) ^{90}Sr/g bodyweight i p	Day 15 Hormone mg s c	Day 30 Hormone mg s c	Day 45 Hormone mg s c	Day 60 Hormone mg s c
A	50	—	14 8 kBq (0 4 μCi)	—	—	—	—
B (Deca Durabol)	50**	0 10	14 8 kBq (0 4 μCi)	—	0 10	—	0 10
C (Estradurin)	50*	0 25	14 8 kBq (0 4 μCi)	—	0 25	—	0 25
D (Depomedrone)	50**	1 0	14 8 kBq (0 4 μCi)	1 0	1 0	1 0	1 0

* One animal was lost during the experiment
** Two animals were lost during the experiment

Table 2

Survival time, tumour frequency and tumour induction time

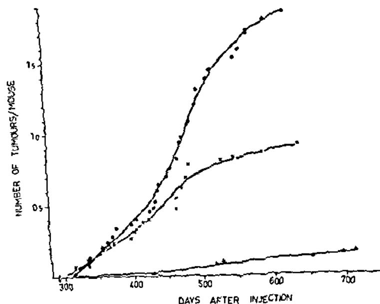
Group	No of mice	Survival (days ± SE)	Bone tumour bearing mice No	Bone tumour bearing mice Per cent	Total No of tumours	No of tumours/mouse	Tumour induction time (days ± SE)	No of lymphoreticular tumours	Induction time
A	50	359 9 ± 15 3	36	72 0	108	2 16	403 3 + 8 9	5	190 2
B	48	348 0 ± 15 2	32	66 7	91	1 90	414 7 ± 9 3	4	245 3
C	49	229 3 ± 9 4	44	89 8	175	3 57	251 9 + 4 1	4	262 0
D	48	452 7 + 22 0	32	66 7	73	1 52	485 3 + 22 7	2	351 0

calculated from the day when ^{90}Sr was given All hormone injections were given subcutaneously The mice were inspected twice daily during the whole experimental period Before autopsy radiography of all mice was performed The carcases were weighed as well as the thymus, spleen and adrenal glands

These organs and both femora, tibiae, humeri, pelvic bones and the spine and sternum were fixed in Stieve's fluid The head was cut longitudinally through its midline and also fixed in Stieve's fluid The bones were decalcified in formic acid 20 %

Ordinary microscopic techniques were used and all sections were stained according to the van Gieson method and with haematoxylin and eosin

The diagnosis of bone tumours was based upon radiographic, post mortem and microscopic findings The number of tumours recorded is a minimum since only the selected bones were microscopically examined



that doses of ^{90}Sr of the present level give a high incidence of this type of tumours in male mice (NILSSON 1970) The angiosarcomas are included since they arise from vessels within the bone marrow Not much difference is found between the various groups of other malignancies (Table 4) The squamous carcinoma in the B group was located in the mucous membrane of the oral cavity The pituitary tumour was of malignant nature as estimated from the morphology and growth characteristics

Causes of death In group A 82 per cent of the mice died from neoplasia, 72 per cent bearing tumours of the skeleton (including angiosarcomas from the bone marrow) and 10 per cent lympho reticular tumours (Table 4) Fourteen per cent of the mice died from liver lesions mainly consisting of multiple necrosis and fattening In the B group about 73 per cent of the mice died from neoplasia (Table 4) Also here was a fairly high frequency of liver degeneration which as in the A-group appeared before the first occurrence of malignancy In the C-group 44 mice had bone tumours at death However, in 15 cases bone sarcoma was not considered to be the true cause of death, since there was a concomitant combination with diseases such as leukaemia, pyometra, inanition and aplasia of the bone marrow In the D group about 10 per cent of the mice died from inanition without tumours in a fairly high age (mean 613 days)

Table 3

Classification of tumours of the skeleton

Group of mice	No of tumours	Type of sarcomas (per cent)				
		Osteoblastic osteosarcoma	Fibroblastic osteosarcoma	Osteoclastic osteosarcoma	Mixed osteosarcoma	Angio-sarcoma
A	30	70 0	23 3	—	—	6 7
B	36	80 6	5 6	2 8	2 8	8 3
C	53	77 4	11 3	7 5	3 8	—
D	41	92 7	2 4	2 4	—	2 4

Table 4

Causes of death

Group of mice	No of dead mice	Osteo-sar-coma	Angio-sar-coma	Squa-mous cell carci-noma	Tumour of the pitui-tary gland	Hepa-toma	Lympho-reti-cular tumour	Liver de-gene-ration	Inani-tion	Pyo metra	Peri toni tis	Not stated
A	50	34	2				5	7				2
B	48	26	3	1	—	1	4	6	2	—	—	5
C	49	29	—			—	4	—	6	6	1	3
D	48	29	1	—	1	2	2	4	5	—	—	4

number of tumours per mouse related to the time after injection of ^{90}Sr is also plotted

The number of tumours per mouse in group C is highly significantly increased (*factor 1 7, p<0 005) over that of group A, whereas in group D there is a strong,* however not significant, (p<0 1) reduction (factor 0 7) of the number of tumours per mouse In the C-group, the true value of the factor is 1 9, since 4 mice died already within 50 days after ^{90}Sr administration In group B the number of tumours per mouse is only slightly less (factor 0 9) than in group A Calculated on the number of tumour bearing mice, only the C-group differs significantly from group A (p<0 05)

Tumour induction time In the C-group the latency time for the bone tumours was on an average 37 5 per cent or 151 days shorter than in the A-group This difference is highly significant (p<0 001) In the D group the induction time instead is prolonged with 20 3 per cent or 82 days (0 01>p>0 001) as compared with the A group

Tumour types The tumour types found appear in Table 3 In all groups osteoblastic osteosarcomas predominate As has been found previously (NILSSON & RÖNNBACK) oestrogenic hormones seem to increase the frequency of osteoclastic osteosarcomas which are very rare when ^{90}Sr is given alone The low frequency of fibroblastic osteosarcomas in female mice of the A-group is also notable since it is known

Table 5 (*cont*)

Mice with osteosarcomas					Mice with reticular tumours	
No of mice	Per cent	Survival (days ± SE)	Total No of tumours	Tumour/mouse	No	Survival (days ± SE)
36	72 0	450 + 13 9	91	1 82	12	240 + 19 4
10	21 3	619 + 36 0	10	0 21	3	464
6	12 2	589	8	0 16	0	
20	47 6	448 + 21 1	39	0 93	0	
0	0	—	—	—	0	
0	0	—	—	—	0	

treated with ^{90}Sr alone (Table 2) Survival time, tumour induction time, and the frequency of lymphoreticular tumours were not influenced at all

As mentioned previously (NILSSON & RÖNNBÄCK) it was anticipated that oestrogenic hormones exerted their promoting action on the ^{90}Sr-carcinogenicity mainly by stimulating the irradiated bone cells to proliferation This means that ^{90}Sr irradiates not only a much more numerous cell population but also a very alert constantly stimulated cell population This seems to indicate that the 'overpopulation' is the most decisive factor, since the greater the population irradiated, the greater the chance for malignant clones to develop An indication of this might also be the high frequency of osteoclastic osteosarcomas after oestrogen treatment, because of the abundancy of these cells attacking '*oestrogenic bone*' This theory seems to fit the results obtained in the corticosteroid series since here instead the irradiated bone cells were influenced by an *inhibitory factor* As indicated previously corticosteroid hormones given continuously for long duration generally induce osteoporosis of the skeleton (NICOLAYSEN) This means that the activity of bone cells is decreased concomitantly with a reduction of their numbers (underpopulation) and as a consequence the bone tissue is devoid of much of its reparative response and proliferative capacity This is probably the main reason why the tumour frequency is diminished

Since both oestrogenic and corticosteroid hormones have lymphocytolytic properties and since ^{90}Sr induced osteosarcomas have been shown to have antigenic capacity (NILSSON et coll 1972) also immunologic factors have to be considered as a cause of the increased tumour frequency after oestrogen treatment However, the antigenicity of these tumours is rather weak and it could therefore be anticipated that the immunologic factors may play only a minor role This seems to be indicated by the fact that osteoblastic osteosarcomas, which seem to be the most antigenic type of ^{90}Sr induced bone tumours, are most numerous in combination with oestrogenic hormones

Table 5

Survival time, tumour frequency and tumour induction time in untreated control mice, ^{90}Sr treated mice and in normal and adrenalectomized and ^{90}Sr + Depomedrone-treated mice

Group of mice (CBA females)	No of mice	Survival (whole material, days ± SE)	Mice without osteosarcomas		
			No of mice	Per cent	Survival (days ± SE)
^{90}Sr only	50	388 ± 17 8	14	28 0	229 ± 15 9
^{90}Sr + Dep (2m)	47	609 ± 21 2	37	78 7	606 ± 25 4
^{90}Sr + Dep (w l)	49	615 ± 18 8	43	87 8	618 ± 20 7
^{90}Sr + Dep (w l) + Op	42	438 ± 19 6	22	52 4	430 ± 33 1
Dep (w l) only	49	636 ± 26 2	49	100 0	636 ± 26 2
Untreated control	50	823 ± 22 7	50	100 0	823 ± 22 7

Dose of ^{90}Sr = 14 8 kBq/g (0 4 μCi/g) bodyweight given as nitrate i p
Dose of Depomedrone (methylprednisolone) 1 mg at each injection
Dep (2 m) Hormone was given every second week for two months
Dep (w l) Hormone was given every second week for the whole life span
Op Adrenalectomy, dorsal route under ether anaesthesia, two weeks before start of experiment Hormone given every second week for the whole life span
Age of mice at start of experiment 75 ± 5 days

Discussion

The present result confirms the previous findings (NILSSON & RÖNNBACK) that oestrogenic hormones have a highly promoting action of the carcinogenicity of ^{90}Sr Glucocorticosteroids were found, on the other hand, to give an opposite effect to that of oestrogenic hormones (Table 2, Fig 1) This finding was considered to be of interest and the Depomedrone experiment was therefore repeated in a somewhat larger scale (Table 5) The depressing tendency on bone sarcoma by glucocorticosteroids found in the first experiment was in the latter not only confirmed but also shown to be clearly significantly separated from that of mice treated with ^{90}Sr alone It was thus found that the tumour frequency was decreased by approximately a factor 10, i e from 1 82 in the group given ^{90}Sr alone to 0 21 and 0 16 in the groups given both Depomedrone and ^{90}Sr (Table 5, Fig 2) The mean tumour induction time was also significantly prolonged (from 450 to 619 and 589 days, respectively) It was also notable that the mice which were treated with Depomedrone survived significantly longer than mice given ^{90}Sr alone Also the frequency of lymphoreticular tumours seemed to decrease after administration of corticosteroids (Table 5) The reason for the large difference of tumour reduction between the first and second experiment is not quite understood, but may be related to the fact that a two year interval separates the experiments Nortestosterone had an insignificant effect on the tumour frequency being 1 90 as compared to 2 16 tumours per mouse in the group

tion of the skeleton (VON WEISSBECKER 1968) In this respect it seems to have an antagonistic effect to glucocorticosteroids and is considered to have a protective effect against factors which depress the cell function of the skeleton (BASSETT et coll)

SUMMARY

Groups of female CBA-mice were given ^{90}Sr (14 8 kBq/g – 0 4 μCi/g – bodyweight) alone or in combination with polyestradiolphosphate, methylprednisolone or nortestosterone, respectively When ^{90}Sr was given in the first combination, the frequency of osteosarcomas was significantly increased whereas the tumour latency time was decreased compared to mice given ^{90}Sr alone In combination with nortestosterone such effects were not found, whereas the combination ^{90}Sr + methylprednisolone resulted in a strong reduction of the osteosarcoma incidence and a prolonged tumour latency time The latter experiment was repeated in a larger experiment whereby the results were confirmed

ZUSAMMENFASSUNG

Gruppen von weiblichen CBA Mausen wurde ^{90}Sr (14,8 kBq/g – 0,4 μCi/g – Korpergewicht) alleine oder in Kombination mit Polyestradiolphosphat, Methylprednisolon oder Nortestosteron gegeben Wenn ^{90}Sr in der ersten Kombination gegeben wurde stieg die Frequenz von Osterosarkomen signifikant, wobei sich die Tumorlatenszeit verglichen mit derjenigen bei Mausen, denen ^{90}Sr alleine gegeben worden war, verringerte In Kombination mit Nortestosteron wurden solche Effekte nicht gefunden, wahrend die Kombination von ^{90}Sr – Methylprednisolon *zu einer bedeutenden* Verminderung der Osteosarkomfrequenz und zu einer verlangerten Tumorlatenszeit fuhrte Die letzteren Experimente wurden in einer grosseren Versuchsreihe wiederholt, wobei sich diese Ergebnisse bestätigten

RÉSUMÉ

Des groupes de souris femelles CBA ont reçu du ^{90}Sr(14,8 kBq/g – 0,4 μCi/g – de poids corporel) seul ou en association avec polyoestradiolphosphate, methylprednisolone ou nortestostérone, respectivement [illegible]
la frequence des osteo [illegible]
de la tumeur est dimi [illegible]
avec la nortestostérone on ne trouve pas d effet semblable, alors que la combinaison du ^{90}Sr avec la methylprednisolone donne une forte reduction de la frequence des osteosarcomes et un temps de latence de la tumeur prolongé Cette derniere experience a ete répetee sur une plus large échelle ce qui a confirme ces *resultats*

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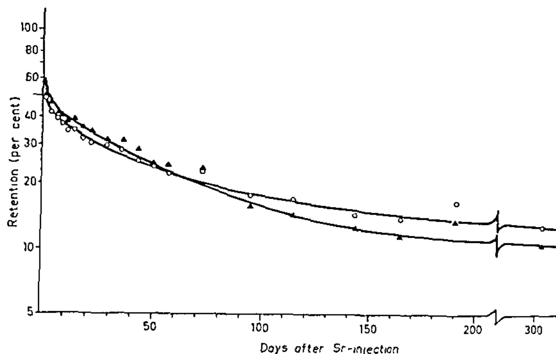


Fig 3 Retention of ^{85}Sr in methylprednisolone treated mice The dose was 2 mg/week during 8 weeks with the first administration 24 hours after the injection of ^{85}Sr ○ = ^{85}Sr ▲ – ^{85}Sr + methylprednisolone (Depomedrone)

The corticosteroid hormones, in spite of their strong lymphocytolytic effect, significantly reduced the tumour frequency. This also seems to indicate that the immune response may play an insignificant role as compared to the depressing effect on the bone cells In this context it should be kept in mind that corticosteroids to a very low degree deplete the cells of the so called thymic dependant areas (LUNDIN & JARPLID)

Another possibility for the increased or decreased tumour frequency in the oestrogen and corticosteroid series, respectively, may be related to an enhanced or diminished accumulation of ^{90}Sr in the bone tissue As regards the oestrogenic hormones RONNBACK & NILSSON (1975) have reported elsewhere that the retention of strontium in oestradiol-treated mice is not higher than in mice given ^{90}Sr alone Also, the administration of Depomedrone only slightly influenced the retention of ^{90}Sr in the skeleton (*Fig 3*), *the irradiation dose to the whole skeleton being only 7 per cent less* than that of the group given ^{90}Sr alone

The reason why adrenalectomy resulted in a higher incidence of tumours than in the intact ^{90}Sr and depomedrone treated animals (factor approx 4 6) is not quite understood, but may be related to an impairment of the adrenalin-chalone complex (BULLOUGH 1968) Whole body external irradiation of intact animals has by FLEMING et coll (1968) also been reported to induce a hyperactivity of the adrenals

Nortestosterone *had no effect on the carcinogenicity of* ^{90}Sr (*Fig 1*) *It has an* anabolic effect on the protein synthesis and influences upon the growth and matura-

FROM THE INSTITUTE OF RADIATION PHYSICS (DIRECTOR PROFESSOR R WALSTAM), KAROLINSKA INSTITUTET, S 104 01 STOCKHOLM, SWEDEN

BUILD-UP EFFECTS AT AIR CAVITIES MEASURED WITH THIN THERMOLUMINESCENT DOSIMETERS

B NILSSON and P O SCHNELL

In the treatment of a tumour in the upper respiratory system with two opposed beams a dose inhomogeneity may occur in the transition zone between air and tissue, causing a dose reduction to cells close to the air cavity and possibly accounting for recurrences (KOSKINEN & SPRING 1973) Evaluation of the dose inhomogeneity has been made for ^{60}Co by EPP et coll (1958) by measuring the build up effect behind air cavities with an ionization chamber Measurements for ^{60}Co with LiF-Teflon disks have been reported by SCRIMGER (1972) who used disks with a thickness of 0 43 mm Preliminary results of measurements with extremely thin LiF-dosimeters (10 μm) have previously been reported (NILSSON et coll 1971) KOSKINEN & SPRING used thin disks (25 μm) for build up measurements They also measured the build down effect i e the decrease in dose depending on absence of scattering material The measurements have now been extended to include roentgen radiation from a 6 MV Varian linear accelerator and from a 42 MV Siemens betatron

Dosimeters LiF dosimeters with a thickness of about 10 μm were used to measure the steep dose gradient By cutting a LiF Teflon rod (LiF-7), diameter 13 mm, with a microtome, dosimeters with an average thickness of 1 6 × 10 $^{-2}$ kg/m^2 with a standard deviation in a group of ten dosimeters of 0 2 × 10 $^{-2}$ kg/m^2, were obtained

A modified Conrad read out instrument (Model 5 100 A) was used to read the dosimeters No difficulty was encountered in obtaining an adequate light response with

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BUILD-UP EFFECTS AT AIR CAVITIES MEASURED WITH THIN THERMOLUMINESCENT DOSIMETERS

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In the treatment of a tumour in the upper respiratory system with two opposed beams, a dose inhomogeneity may occur in the transition zone between air and tissue, causing a dose reduction to cells close to the air cavity and possibly accounting for recurrences (KOSKINEN & SPRING 1973) Evaluation of the dose inhomogeneity has been made for ^{60}Co by EPP et coll (1958) by measuring the build-up effect behind air cavities with an ionization chamber Measurements for ^{60}Co with LiF-Teflon disks have been reported by SCRIMGER (1972) who used disks with a thickness of 0 43 mm Preliminary results of measurements with extremely thin LiF-dosimeters (10 μm) have previously been reported (NILSSON et coll 1971) KOSKINEN & SPRING used thin disks (25 μm) for build-up measurements They also measured the 'build-down effect', i e the decrease in dose depending on absence of scattering material The measurements have now been extended to include roentgen radiation from a 6 MV Varian linear accelerator and from a 42 MV Siemens betatron

Dosimeters LiF dosimeters with a thickness of about 10 μm were used to measure the steep dose gradient By cutting a LiF-Teflon rod (LiF-7), diameter 13 mm, with a microtome, dosimeters with an average thickness of $1\,6 \times 10^{-2}$ kg/m² with a standard deviation in a group of ten dosimeters of $0\,2 \times 10^{-2}$ kg/m², were obtained

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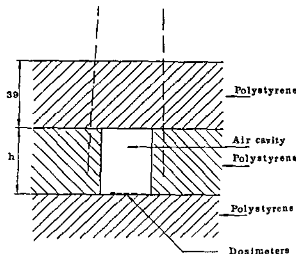


Fig 1 Irradiation geometry for the build-up measurements The cavity depth varied between 9 and 39 mm

absorbed doses of about 2 Gy (200 rad) For reading the dosimeters were pressed against the planchette under a micro-cover glass

The sensitivity and reproducibility of the LiF-dosimeters are strongly depending on pre- and post-annealing procedures The read-out process should, if possible, be used as the only high temperature pre-annealing for LiF-dosimeters (CARLSSON 1969, MÅRTENSSON 1969) With the thin dosimeters heating and cooling can be made rapidly and reproducibly, only a short time at high temperature is needed to empty all the filled traps This will give a low standard deviation One problem with not using extra pre- and post-annealing is fading To overcome this, every dosimeter was read out at a fixed time after the irradiation To avoid dosimeter sensitivity changes, depending on differences in total radiation dose, the dosimeter was placed at different depths from time to time

The dosimeters were calibrated individually The average value of the standard deviation of the calibration constant for a group of 20 dosimeters was 2 7 per cent

Experimental method A geometry similar to the one used by EPP et coll was used A polystyrene phantom, 300 mm × 300 mm, was constructed in which air cavities of different sizes could be arranged The thickness above the air cavities was 39 mm (Fig 1) The thickness below any cavity was more than 100 mm in order to minimize the dependence of back scattering

During the measurements, polyester films of different thicknesses were placed above the dosimeters The best method at depth dose measurements of this type would be to irradiate many dosimeters at the same time, in an attempt to obtain the whole depth dose curve in one measurement However, if the dosimeters are not of the same material as the phantom they will disturb the radiation beam In the present experiments with a polystyrene phantom it was concluded that not more than four measuring points should be used at the same time This implied a total dosimeter thick-

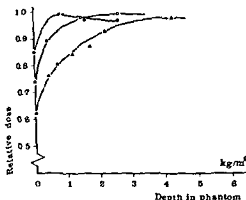


Fig 2. Relative dose for ^{60}Co γ-radiation with different cavity depths Field size 40 mm × 40 mm. SSD 800 mm. (●) – 9 × 30 × ∞, (○) – 21 × 30 × ∞, (△) – 39 × 30 × ∞

ness of 6.4×10^{-2} kg/m² At every point 2 to 3 dosimeters were placed beside each other in the homogeneous centre of the beam The results were obtained on the assumption that the output from each dosimeter was proportional to the dose at the depth where the dosimeter was located It cannot be excluded that the electron spectrum may be varying at the surface and at greater depths, with different response in the dosimeters This effect, which is probably small, has been neglected in the present investigation The surface dose was the dose obtained by the dosimeters situated on the surface of the cavity

Results

The results obtained for ^{60}Co are presented in the Table (two standard errors indicated) and Fig 2 From the Table it may be seen that the relative surface doses

Table

BUR^{-1} and BDR^{-1} for different cavity depths and radiation qualities Field size 40 mm × 40 mm Two standard errors are indicated BDR^{-1} is defined as the ratio of the absorbed dose at the surface in front of the cavity to the absorbed dose at the same point without the cavity BUR^{-1} is defined as the ratio of the absorbed dose at the surface behind the cavity to the absorbed dose obtained by extrapolating the depth dose curve back to the cavity surface

Air cavity (depth × width × length)	^{60}Co BUR^{-1} Epp et coll	^{60}Co BUR^{-1} Present investigation	^{60}Co BDR^{-1}	6 MV BUR^{-1}	6 MV BDR^{-1}	42 MV BUR^{-1}	42 MV BDR^{-1}
39 × 30 × ∞	0.84	0.62 ± 0.04	0.89 ± 0.04	0.67 ± 0.04	0.87 ± 0.04	0.76 ± 0.04	0.95 ± 0.04
21 × 30 × ∞	0.92	0.74 ± 0.04	0.89 ± 0.04	0.79 ± 0.04	0.87 ± 0.04	0.76 ± 0.04	0.92 ± 0.04
9 × 30 × ∞	0.97	0.85 ± 0.04		0.89 ± 0.04		0.88 ± 0.04	

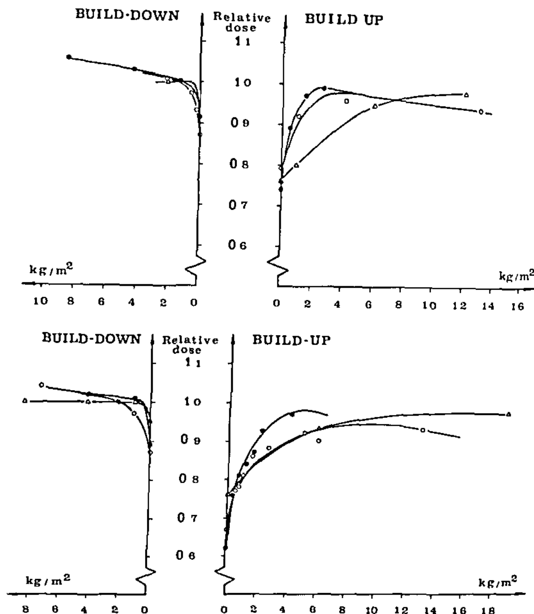


Fig 3 The build-down and build up effects around an air cavity irradiated with different radiation qualities Field size 40 mm × 40 mm Top Cavity depth 21 mm Bottom Cavity depth 39 mm (●) – ^{60}Co, (○) 6 MV, (△) – 42 MV

obtained by EPP et coll are considerably higher than those obtained in the present experiments, from about 15 to 30 per cent This may be explained by the fact that the detector used by EPP et coll was an ionization chamber with 10 mm diameter, 1 5 mm depth and a thin entrance window (10^{-2} kg/m²) Because of its depth the detector will record electrons from the surrounding material which will not hit the thin thermoluminescent dosimeter in the present experiments

The results of SCRIMGER and the present ones agree fairly well with the exception of the surface dose value of SCRIMGER, which is higher than the present one This

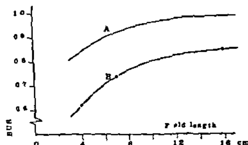


Fig 4 Relative surface dose (BUR^{-1}) as a function of field dimension parallel to the cavity length Field width 40 mm A – EPP et coll B – Present investigation Cavity 39 × 30 × ∞

probably depends on the linear extrapolation from the first measuring point to the surface, used by SCRIMGER According to the present measurements such a linear extrapolation does not seem to be correct

The values obtained by KOSKINEN & SPRING are also slightly higher than the present ones which might be due to the difference in thickness of the dosimeters

For the 6 MV linear accelerator and the 42 MV betatron about the same BUR^{-1} values as for ^{60}Co were obtained (Table, Fig 3) For these higher energies lower BUR^{-1} values could possibly be expected That this was not the case is probably due to a greater electron contribution from the material located above the cavity, as compared to the situation with ^{60}Co gamma radiation

Because of the somewhat surprising results that the same BUR^{-1} was obtained for cavity depths of 21 and 39 mm for 42 MV roentgen rays some complementary measurements were made for a cavity depth of 30 mm These measurements confirm the previous results A separate investigation on the electron contribution to the absorbed dose from different parts of the cavity indicates that the decrease in electron contribution to the surface dose from material above the cavity is balanced by an increase in scattering from the cavity walls

With broader beams the relative surface dose will be higher The relative surface dose as a function of the length of the radiation field for ^{60}Co radiation appears in Fig 4 Curve A represents values obtained by EPP et coll Curve B is based on the present experiments with values considerably lower than the previous ones

In treatment of malignant tumours in the upper respiratory tract two opposed beams are often used In this situation it is necessary also to take into consideration the build down effect depending on absence of back scattering material The build down and the build up effects for three radiation qualities appear in Fig 3 Th[illegible]

[illegible] about the same dose reduction as in the present investigation This means that the total effect is smaller than can be estimated only from the build up effect As an example the effects of the build up and the build down was combined for the phantom with a cavity depth of 39 mm with the use of two opposed beams This

results in the following doses at the cavity surface, normalized to the maximum dose in the phantom ^{60}Co 74 per cent, 6 MV 77 per cent, and 42 MV 87 per cent

SUMMARY

The build up and build down situation around air cavities of various size in a polystyrene phantom was evaluated by measurements with LiF Teflon disks with a thickness of about $1\ 6 \times 10^{\ 2}$ kg/m^2 The measurements demonstrate that when irradiating with two opposed beams the surface dose at the cavity (depth 39 mm) is 74% of the maximum dose for ^{60}Co 77% for 6 MV and 87% for 42 MV roentgen radiation

ZUSAMMENFASSUNG

Die Build up und Build down Situation um Luftkavitaten verschiedener Grosse in einem Polystyrenphantom wurde durch Messungen mit LiF Teflon Scheiben von einer Dicke von etwa $1\ 6 \times 10^{\ 2}$ kg/m^2 bestimmt Die Messungen zeigten dass die Oberflachendosis einer Kavitat (Tiefe 39 mm) bei Bestrahlung mit zwei gegensatzlichen Strahlenbundeln fur ^{60}Co 74% der maximalen Dosis fur 6 MV Rontgenstrahlen 77% und fur 42 MV Rontgenstrahlen 87% betragt

RESUME

La distribution du « build up » et du « build down » autour de cavités d air de différentes dimensions dans un fantôme de polystyrène a été étudiée par des mesures faites avec des disques de LiF Teflon ayant une épaisseur d environ $1\ 6\ \ 10^{\ 2}$ kg/m^2 Les mesures montrent que quand on irradie par deux faisceaux opposés la dose à la surface de la cavité (profondeur 39 mm) est *pour le ^{60}Co de 74% de la dose maximale et pour le rayonnement roentgen* de 6 MV de 77% et pour le rayonnement roentgen de 42 MV de 47%

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of pre annealing on the precision

NILSSON B SCHNELL P O and WAL
kaviteter (In Swedish) Presented at the 31st Meeting of the Scandinavian Radiological Society Reykjavik 1971

SCRIMGER J W Effect of air gap on absorbed dose in tissue Radiology 102 (1972) 171

FROM THE DEPARTMENTS OF PATHOLOGY AND PSYCHIATRY, UNIVERSITY OF UMEÅ, S-901 87 UMEÅ, AND THE DEPARTMENT OF PSYCHIATRY, UNIVERSITY OF UPPSALA, S-752 20 UPPSALA, SWEDEN

LATE EFFECTS ON RABBIT BRAIN MORPHOLOGY AND MONOAMINE METABOLITES PRODUCED BY ^{60}Co-IRRADIATION

R ADOLFSSON, C-G GOTTFRIES, O HASSLER, B E ROOS and B WINBLAD

The lesions produced in the brain by ionizing radiation are known to be time and dose dependent (BERG & LINDGREN 1958, CAVENESS et coll 1967, SAMORAJSKI et coll 1970, CARSTEN et coll 1970, HSU & SAMORAJSKI 1974) Furthermore, when discussing radiation sensitivity or resistance, reference to method and species used must be made (ZEMAN 1968) The sharp brain, as an extreme example, is very resistant to radiation OLSSON et coll (1972) noticed little parenchymal change after single exposure of 300 [illegible]

[illegible] Loss of neurons occurs after irradiation (SAMORAJSKI et coll, BRIZZEE 1973) A positive correlation was found between loss of neurons and length of life The structural changes of the brain parenchyma and vessels have been investigated in detail (DUGGER et coll 1954, BROWNSON 1961, FRANKE & LIERSE 1965, MAXWELL & KRUGER 1965, HASSLER 1966, HASSLER & MOVIN 1966, OLSSON et coll 1975), as well as the time relationship between vascular and parenchymal injury It is customary to differentiate the specific response to radiation into two stages an acute stage (the first weeks after the irradiation) with more or less complete recovery and a delayed stage (beginning 4 to 5 months after the irradiation and probably lasting for years) with irreversible destruction of vessels and brain parenchyma

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results in the following doses at the cavity surface, normalized to the maximum dose in the phantom· ^{60}Co 74 per cent, 6 MV 77 per cent, and 42 MV 87 per cent

SUMMARY

The build-up and build-down situation around air cavities of various size in a polystyrene phantom was evaluated by measurements with LiF-Teflon disks with a thickness of about 1.6×10^{-2} kg/m² The measurements demonstrate that when irradiating with two opposed beams the surface dose at the cavity (depth 39 mm) is 74% of the maximum dose for ^{60}Co, 77% for 6 MV and 87% for 42 MV roentgen radiation

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Die Build-up und Build-down Situation um Luftkavitaten verschiedener Grosse in einem Polystyrenphantom wurde durch Messungen mit LiF-Teflon Scheiben von einer Dicke von etwa $1{,}6 \times 10^{-2}$ kg/m² bestimmt Die Messungen zeigten, dass die Oberflachendosis einer Kavitat (Tiefe 39 mm) bei Bestrahlung mit zwei gegensatzlichen Strahlenbundeln fur ^{60}Co 74% der maximalen Dosis, fur 6 MV Rontgenstrahlen 77% und fur 42 MV Rontgenstrahlen 87% betragt

RÉSUMÉ

La distribution du « build up » et du « build-down » autour de cavités d'air de différentes dimensions dans un fantôme de polystyrène a été étudiée par des mesures faites avec des disques de LiF-Teflon ayant une épaisseur d'environ 1,6 10^{-2} kg/m² Les mesures montrent que quand on irradie par deux faisceaux opposés la dose à la surface de la cavité (profondeur 39 mm) est, pour le ^{60}Co, de 74% de la dose maximale, et pour le rayonnement roentgen de 6 MV de 77% et pour le rayonnement roentgen de 42 MV de 47%

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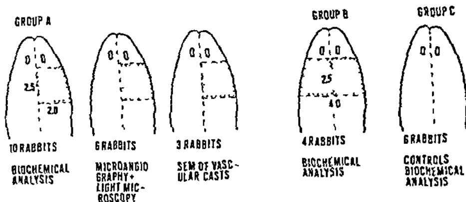


Fig 1 In group A the irradiated field over the right hemisphere (dashed area) was 2.5 cm × 2.0 cm Dose 29 6 Gy In group B both hemispheres were exposed with 20 Gy, irradiation field 2 5 cm × 4 0 cm. Different means of post irradiation investigation are indicated for the various groups

from a kilotherapy unit The exposure in the centre of the field was 29 6 Gy (2 960 rad) and the dose 1 cm beneath the skin was calculated to 23 Gy (2 300 rad) (Clinical Dosimetry 1963) Group A was divided into 3 subgroups, one consisting of 10 rabbits for biochemical analysis, one of 6 rabbits for microangiography and light microscopy and one group of 3 rabbits for assessment of vascular casts by scanning electron microscopy (SEM)

Group B consisted of 4 animals irradiated over both hemispheres with 20 Gy (2 000 rad), the dose 1 cm beneath the skin being 16 Gy (1 600 rad) The brains were used for biochemical analysis

Group C consisted of 6 animals not exposed to irradiation and served as controls

During the irradiation the animals were anesthetized by Nembutal (Abbott) The rabbits were kept in individual cages and fed rabbit chow and water ad lib In group A, 2 animals (Nos 16 and 18) had to be killed after 3 1/2 months because of paresis of the legs and difficulty in eating They were included in the group for biochemical analysis

Six months after the irradiation the animals were decapitated and treated as follows

Biochemical analysis The brains of the 10 rabbits in group A and all in groups B and C were dissected immediately after death From seven parts of both brain halves (Tables 1 to 3) pieces were cut out and immediately frozen on dry ice and stored at −20 C until assayed Specimens from irradiated and non irradiated pairs of animals were pooled to get enough material for biochemical assay The concentrations of the metabolites of 5-HT and DA, viz 5-hydroxyindoleacetic acid (5-HIAA) and homovanillic acid (HVA) were determined, 5-HIAA according to a method of JANSSON & LEVANDER (1970) and HVA according to a method described by ANDEN et coll (1963) and KORF et coll (1971)

(ARNOLD et coll 1954, BROWNSON, HASSLER & MOVIN) The onset of symptoms or signs after the irradiation, for example the appearance of seizures, may be delayed, as demonstrated by CAVENESS et coll (1964) in a long term experiment of *Macula Mulatta* However, there is no reason to believe that the interval between the early and delayed effects on the brain parenchyma or the interval between irradiation and the appearance of clinical manifestations is 'silent' According to CAVENESS et coll (1964) there may be exacerbations and partial remissions rather than a steady progression By careful evaluation of the dendritic ramification after a single dose of 35 Gy (3 500 rad) to visual cortex of the right occipital lobe in monkies CAVENESS et coll (1967) observed a biphasic EEG response with a first maximum after 6 weeks and a second phase beginning after 18 to 22 weeks After 50 weeks of observation (CARSTEN et coll) a bilateral depression developed, i e also on the non-irradiated side an EEG-appearance of depression was observed Despite this finding no microscopic abnormality on the non-irradiated side was disclosed The pathogenesis of radiation-induced injury of the vessels (vascular hyperpermeability, endothelial swelling) disintegration of glial cells and loss of neurons is not completely understood PAUSESCU et coll (1973) proposed that an excessive elevation of the biogenic amines may be responsible for these structural changes In a short term experiment (rat, single dose 40 Gy, 4 000 rad) by DAHLSTRÖM et coll (1973) it was shown by means of fluorescence technique that the vesicles in the nerve terminals leaked out their content The apparent effects on the nerve terminals with alterations in the amine content, has biochemically been investigated by several authors but the results (Table 4) are not uniform Different animals, variation in dosis and type of radiation and different lengths of observation time may be contributing factors A relationship between lowering of 5 hydroxy tryptamine (5-HT) concentration and the appearance of convulsive seizures has been considered of importance (BONNYCASTLE et coll 1957, DE LA TORRE et coll 1970, CHADWICK et coll 1975) The previous biochemical reports have most often dealt with acute or short time effects on the levels of monoamines Furthermore the monoamine analysis data have been expressed as total brain concentration, which must be of less value when considering the uneven distribution of the monoamines The aim of the present investigation was to disclose the long term effects of irradiation on the concentration of the principle metabolites of dopamine (DA) and 5 HT in well defined parts of the rabbit brain Applying a new method for demonstrating brain vessels by scanning electron microscopy, an attempt to demonstrate telangiectases was made and the results were compared with those of microangiography, previously evaluated in this respect (HASSLER & MOVIN) To assess the destructive effect of irradiation to the brain parenchyma, conventional light microscopy was applied

Material and Methods

Irradiation (Fig 1) In group A, which consisted of 19 rabbits, the animals were irradiated vertically through the skull over the right hemisphere with ^{60}Co-irradiation

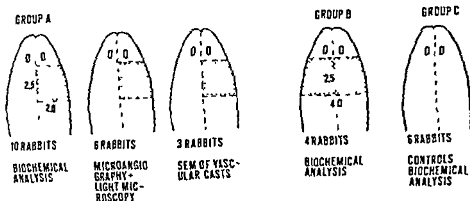


Fig. 1 In group A the irradiated field over the right hemisphere (dashed area) was 2.5 cm × 2.0 cm. Dose 29.6 Gy. In group B both hemispheres were exposed with 20 Gy, irradiation field 2.5 cm × 4.0 cm. Different means of post irradiation investigation are indicated for the various groups

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Table 1

Concentrations of the metabolites 5 hydroxyindolacetic acid (5-HIAA) and homovanillic acid (HVA), expressed in ng/g wet tissue, in different parts of the brains of the rabbits not exposed to irradiation The brains of paired rabbits were pooled to get enough material

5 HIAA					HVA		
Rabbit No	Parietal cortex	Hippo-campus	Thala-mus	Cere-bellum	Caudate nucleus	Mesen cephalon	Frontal cortex
10+15	253	427	1 043	84	4 697	285	349
11+13	256	194	953	116	2 830	263	269
12+14	169	224	1 325	48	14 120	423	236
16+18	170	610	1 450	200	14 730	310	110
17+19	280	261	1 038	11	7 851	279	386
20+21	191	371	1 019	88	5 000	358	442
20+21	344	386	840	98	6 385	316	713
22+25	253	371	1 124	124	4 113	604	—
22+25	292	465	1 115	128	2 820	249	189
26+28	271	372	1 248	99	4 800	305	282
26+28	255	358	1 115	72	5 630	154	256

Light microscopy From group A, specimens of the brains of 6 animals were examined after staining by haematoxylin-eosin, van Gieson's and Nissl's stains and McMahon's myelin stain It was possible to obtain material from the same rabbits as used for microangiography

Scanning electron microscopy Vascular casts of the brain vessels of three rabbits (Nos 7, 8, 9) prepared with resin injection were examined according to a method described by MURAKAMI (1971) A methacrylic methyl ester was injected into the thoracic aorta After hardening of the plastic the surrounding brain tissue was removed with concentrated *NaOH*, sometimes supplemented by ultrasonic treatment The plastic casts of the blood vessels were prepared for mounting on specimen stubs The casts were coated with gold in a vacuum evaporator A Cambridge Stereoscan S4 microscope operated at 5 to 10 kV was used

Microangiography Six rabbits in group A were prepared for microangiography by a method described by HASSLER & MOVIN Thin slices of the brain obtained by frontal sectioning were then examined by light microscopy

Results

Clinical observations In group A minor neurologic sequels were observed An unsteady gait and a slight deviation of the head to the right irradiated side was often



Fig 2 Section of the right temporal lobe of a rabbit 6 months after irradiation with 29 6 Gy Disorganization of the brain parenchyma with cell loss gliosis and oedema is evident A relatively large vessel probably telangiectatic is partly occluded by thrombotic material (H & E ×250)

present No convulsions occurred The external effects of irradiation were epilation keratitis and conjunctival adherences These findings were less evident in group B where the animals received a lower dose The medium weight gain in group A was 0 45 kg in group B 1 5 kg and for the controls 1 9 kg

Macroscopy The lepto meninges were thickened but were easily removed On dissection petechial haemorrhages and local atrophic abnormalities of the caudate nucleus with secondary ventricular dilation were a constant finding in group A Haemorrhages were observed in the hippocampus caudate nucleus and in the white matter surrounding the lateral ventricle on the irradiated side No gross changes were observed in the cortex Cystic spaces were observed on the cut surfaces when slicing the brain In group B the changes were of the same distribution bilaterally but less marked

Microscopy From the non irradiated part of the brain no morphologic abnormality was observed Examined parts from the irradiated region had lost their normal structure the disorganization being most apparent in the white matter Intermingled necrosis haemorrhage and cystic degeneration were constantly observed in the parenchyma Especially in connection with the necroses perivascular inflammation and often fibrinoid necroses in the vascular wall were found Endothelial swelling and proliferation was common Some dilatated vessels were occluded by thrombotic material (Fig 2) The astroglial elements were hypertrophic and atypical forms occurred Nerve cell loss and abundant gliosis existed

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Concentrations of the metabolites 5 hydroxyindolacetic acid (5-HIAA) and homovanillic acid (HVA) expressed in ng/g wet tissue, in different parts of the brains of the rabbits not exposed to irradiation The brains of paired rabbits were pooled to get enough material

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Table 2

Concentrations of the metabolites 5-HIAA and HVA (expressed in ng/g wet tissue) in different parts of the brains of the rabbits exposed to ^{60}Co-irradiation (1 Gy – 100 rad) The brains of paired rabbits were pooled to get enough material

5-HIAA						HVA		
Rabbit No	Irradiation dose (Gy)	Parietal cortex	Hippocampus	Thalamus	Cerebellum	Caudate nucleus	Mesencephalon	Frontal cortex
10+15	29 60	181	223	2 008	199	2 248	340	210
11+13	29 60	248	127	1 127	125	3 147	260	—
12+14	29 60	173	181	928	35	9 040	284	421
16+18	29 60	440	540	1 470	100	7 100	370	420
17+19	29 60	240	85	1 119	55	7 277	343	440
23+24	20 00	144	144	1 335	87	4 870	306	177
23+24	20 00	176	406	1 364	111	4 556	217	85
27+29	20 00	276	606	1 553	113	4 690	378	520
27+29	20 00	258	578	1 442	123	3 840	314	406

Table 3

Average concentrations of the metabolites 5-HIAA and HVA (expressed in ng/g wet tissue) in non irradiated and irradiated parts of the brains of the rabbits Statistical evaluation with Student's t test

Parts of brain	Control group			Irradiated group			T-test	
	M	*SD*	*n*	*M*	*SD*	*n*	*t*	*p* <
5-HIAA								
Thalamus	1 115±	172	11	1 372±	311	9	2 338	0 05
Parietal cortex	249±	53	11	237±	89	9	0 350	n s
Hippocampus	367±	116	11	321±	211	9	0 621	n s
Cerebellum	97±	48	11	105±	47	9	0 385	n s
HVA								
Caudate nucleus	6 634±	4 115	11	5 196±	2 186	9	0 942	n s
Mesencephalon	322±	115	11	312±	52	9	0 239	n s
Frontal cortex	323±	167	8	325±	164	8	0 019	n s

Biochemical analysis Comparison between the levels of the monoamine metabolites in the non-irradiated animals (Nos 20, 21, 22, 25, 26, 28) and the non-irradiated halves of the brains in group A (Nos 10 to 19) was made No significant differences were found between those groups (Table 1) Consequently all values were brought into a control group The 5-HIAA and HVA-levels in those animals where the whole brain had been exposed (Nos 23, 24, 27, 29) compared with those who had had their right halves of the brain irradiated (Nos 10 to 19) were not significantly different


Fig 3


Fig. 4

Fig 3 Microangiogram from the non irradiated temporal lobe of a rabbit, regular distribution of *the brain vessels* (20)

Fig 4 Microangiogram from the irradiated right temporal lobe of the same rabbit as in Fig 3, 6 months after receiving 29 6 Gy Telangiectases (two upper arrows), leakage of contrast medium from injured vessels (arrows in right lower corner) (35)


Fig 5


Fig 6

Fig 5 SEM of casts of small brain vessels *from the* non irradiated temporal lobe (white matter) of a rabbit (200)

Fig 6 SEM of casts of small brain vessels from the temporal lobe (*white matter*) of the same rabbit as in Fig. 5 6 months after receiving 29 6 Gy Fusiform dilatations of vessels, representing telangiectases (400)

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Concentrations of the metabolites 5-HIAA and HVA (expressed in ng/g wet tissue) in different parts of the brains of the rabbits exposed to ^{60}Co-irradiation (1 Gy = 100 rad) The brains of paired rabbits were pooled to get enough material

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Hippocampus	367 ±	116	11	321 ±	211	9	0 621	n s
Cerebellum	97 ±	48	11	105 ±	47	9	0 385	n s
HVA								
Caudate nucleus	6 634 ±	4 115	11	5 196 +	2 186	9	0 942	n s
Mesencephalon	322 ±	115	11	312 ±	52	9	0 239	n s
Frontal cortex	323 ±	167	8	325 ±	164	8	0 019	n s

Biochemical analysis Comparison between the levels of the monoamine metabolites in the non-irradiated animals (Nos 20, 21, 22, 25, 26, 28) and the non-irradiated halves of the brains in group A (Nos 10 to 19) was made No significant differences were found between those groups (Table 1) Consequently all values were brought into a control group The 5-HIAA and HVA-levels in those animals where the whole brain had been exposed (Nos 23, 24, 27, 29) compared with those who had had their right halves of the brain irradiated (Nos 10 to 19) were not significantly different

Table 4 (cont)

Author	Animal	Dose (irradiation)	Analysis (part of brain)	Irradiated field	Autopsy after irradiation	Results
HSU & SAMORAJSKI 1974	Mouse	5 000 10 000 15 000 20 000 rad (deuteron irradiation)	NA tyrosine hydroxylase Cortical and hypothalamic gray matter	Head	12, 40 days 12 5 months	↑Tyrosine hydroxylase with 5 K after 12 days and with 10–20 K at all times
CATRAVAS & MCHALE 1975	Rat	18 000 rad (neutron- and γ irradiation)	MAO cerebellum, cortex hypothalamus hippocampus	Body	4 40 180 min	↑MAO (γ rays) at all times ↓MAO (neutron) at all times

Abbreviations used 5 HT 5 hydroxytryptophan 5 HIAA = 5 hydroxyindolacetic acid NA = Noradrenalin A Adrenalin DA = Dopamine DOPA = Dihydroxyphenylalanine DOMA = 3 4-dihydroxymandelic acid MAO = Monoamine oxidase

* Striate area 17 of the visual cortex

(Table 2) and were collected in an irradiated group In the statistical analysis between these constructed groups no significant differences were found The 5 HIAA levels in the thalamus in the irradiated group were somewhat higher than in the control group although statistically not convincing (p 0 05 Student s t test, Table 3)

Microangiography In the non irradiated half of the brain a normal distribution and appearance of the brain vessels was observed (Fig 3) In 3 of the 6 irradiated animals typical telangiectases had developed and in some regions leakage of contrast medium was observed (Fig 4) These changes predominated in the white matter of the cerebrum The telangiectases were especially well developed in the neighbourhood of the radiation necroses

Scanning electron microscopy of vascular casts In casts from non irradiated parts of the brain no structural abnormalities of the vessels appeared (Fig 5) In the irradiated brain half partly fusiform dilatations of the vessels were demonstrated by by the casts (Fig 6) In some regions extravasal deposits of plastic material were found indicating vascular radiation injury with subsequent leakage

Discussion

The rabbit tolerance to the radiation doses used in this experiment is high (BERG & LINDGREN HASSLER & MOVIN) only two animals had to be killed earlier than planned

Table 4

Review of eleven previous reports on effects of irradiation on monoamines, monoamine metabolites and related enzymes in the brain after irradiation. In the table only data which are relevant to the present investigation are presented

Author	Animal	Dose (irradiation)	Analysis (part of brain)	Irradiated field	Autopsy after irradiation	Results
Palaic & Supek 1965	*Rat*	*900 rad* (Rtg-irradiation)	*5-HT, 5-HIAA* Brain-stem	*Head*	*Immediately* and after 3, 24, 48 hours	*↑5-HT imme-* diately after ↓5-HT at 48 hours
Palaic & Supek 1965	Rat	900 rad (Rtg-irradiation)	5-HT, 5-HIAA Brain-stem	Body	Immediately and after 3, 24, 48 hours	No significant changes
Palaic & Supek 1966	Rat	900 rad (Rtg-irradiation)	5-HT, NA Whole brain	Head	3, 24 hours	↓5-HT at 24 hours ↓NA at 3 hours
Ordy et coll 1968	Mouse	500, 5 000, 10 000 rad (deuteron-irradiation	5-HT, NA Whole brain	Head	16 months	↓5-HT with 10 000 rad at 16 months
Van Woert & Korb 1970	Rat	1 800 rad (Rtg-irradiation)	NA, tyrosine hydroxylase Whole brain	Body	12, 24, 48, 72, 84 hours	No significant changes
Hsu et coll 1971	Monkey	10 000, 20 000 rad (proton irradiation)	NA, DA N caudatus, hypothalamus, hippocampus, putamen, cerebellum, brain-stem	Head*	6 months	↓NA at 6 months except for cerebellum
Ankov & Zhelyazkov 1971	Rat	900 rad (Rtg-irradiation)	NA, A DA Whole brain	Body	30, 60, 180 min	↑DA at 60 min ↓NA at all times
Dahlstrom et coll 1973	Rat	4 000 rad (Rtg irradiation)	NA, DA Whole brain	Head	24 hours, 7 days	No significant changes
Pausescu et coll 1973	Rabbit	400 rad (^{60}Co-irradiation)	NA, A, DA DOPA, 5-HT, DOMA, MAO, dopa decarboxyl Cortical and hypothalamic gray matter	Body	24 hours	↑NA, ↑A ↑DA ↑DOPA ↑DOMA ↑MAO ↑dopa decarboxylase

Table 4 (*cont*)

Author	Animal	Dose (irradiation)	Analysis (part of brain)	Irradiated field	Autopsy after irradiation	Results
HSU & SAMORAJSKI 1974	Mouse	5 000, 10 000 15 000, 20 000 rad (deuteron irradiation)	NA, tyrosine hydroxylase Cortical and hypothalamic gray matter	Head	12, 40 days 12.5 months	↑Tyrosine hydroxylase with 5 K after 12 days, and with 10-20 K at all times
CATRAVAS & MCHALE 1975	Rat	18 000 rad (neutron and γ irradiation)	MAO, cerebellum, cortex, hypothalamus hippocampus	Body	4, 40, 180 min	↑MAO (γ rays) at all times ↓MAO (neutron) at all times

Abbreviations used 5 HT = 5 hydroxytryptophan 5-HIAA = 5 hydroxyindolacetic acid NA = Noradrenalin A = Adrenalin DA = Dopamine DOPA = Dihydroxyphenylalanine DOMA = 3,4 dihydroxymandelic acid MAO = Monoamine oxidase

* Striate area 17 of the visual cortex

(Table 2) and were collected in an irradiated group In the statistical analysis between these constructed groups no significant differences were found The 5-HIAA levels in the thalamus in the irradiated group were somewhat higher than in the control group, although statistically not convincing ($p < 0.05$, Student's t-test, Table 3)

Microangiography In the non irradiated half of the brain a normal distribution and appearance of the brain vessels was observed (Fig 3) In 3 of the 6 irradiated animals typical telangiectases had developed and in some regions leakage of contrast medium was observed (Fig 4) These changes predominated in the white matter of the cerebrum The telangiectases were especially well developed in the neighbourhood of the radiation necroses

Scanning electron microscopy of vascular casts In casts from non irradiated parts of the brain, no structural abnormalities of the vessels appeared (Fig 5) In the irradiated brain-half, partly fusiform dilatations of the vessels were demonstrated by the casts (Fig 6) In some regions extravasal deposits of plastic material were found, indicating vascular radiation injury with subsequent leakage

Discussion

The rabbit tolerance to the radiation doses used in this experiment is high (BERG & LINDGREN, HASSLER & MOVIN), only two animals had to be killed earlier than planned

because of neurologic sequels With the dose applied all animals gained weight, although the irradiated ones less than the controls Loss of weight is a well known effect of irradiation, sometimes depending on refusal to eat and drink Several authors have reported a shortened life-expectancy after irradiation which has been used as a tool for evaluating the process of ageing (CURTIS 1963, SAMORAJSKI et coll, ORDY et coll 1971)

The delayed irreversible morphologic alterations indicated by the appearance of the telangiectases were demonstrated by HASSLER & MOVIN to appear about 4 months after ^{60}Co-irradiation of the brain of the rabbit In the present experiment similar vascular dilatations were demonstrated 6 months after irradiation by using scanning electron microscopy

The scanning technique gives a three-dimensional image and permits a higher magnification, but, compared to microangiography, has the drawback of making it impossible to confirm the findings by light microscopy of the same specimen Another disadvantage with the scanning method of vascular casts is the difficulty of exact localization of the telangiectases in the brain parenchyma It is known from microangiographic reports that the telangiectases most frequently are found in the periphery of the radiation necroses and in the white matter (HASSLER & MOVIN, HASSLER)

It has been shown that the brain is considerably more sensitive to ionizing radiation than revealed by morphologic abnormalities (CAVENESS et coll 1967, ORDY et coll 1968, CARSTEN et coll, HSU et coll 1971) In these and other reports (Table 4) the concentrations of various neurotransmitters and their metabolites were estimated, particularly in short term experiments An injury to the vesicles in the nerve terminals, which by no doubt occurs after irradiation, has been shown to be reversible (DAHLSTRÖM et coll) Surprisingly this apparently destructive effect on the vesicles was not revealed by any changes in the concentrations of NA or DA Others (ANKOV & ZHELYAZKOV 1971) have found decreased concentration of NA soon after the irradiation but the experimental conditions were not the same (Table 4)

Opinions on the effects of 5-HT-turnover differ The concentration of 5-HIAA did not change after head or body irradiation of the rat (PALAIC & SUPEK 1965) No reports on HVA and irradiation have been found in the literature However, the evaluation of the results is complicated by the fact that several enzymes responsible for synthesis and degradation of the monoamines seem to be activated, i e dopa-decarboxylase, tyrosine hydroxylase and monoamine oxidase (PAUSESCU et coll, CATRAVAS & MCHALE 1975) Furthermore, the analyses were most often done on whole brain preparation expressed in wet weight per gram tissue, thus, eventually regional changes of the concentrations disappear In the nearest time after irradiation the brain increases in weight due to an oedema HSU & SAMORAJSKI found an increase in brain weight 12 days after irradiation at 50 or 100 Gy of deuteron irradiation but after 40 days the brain weight had normalized At higher doses, 150 or 200 Gy, an increase both after 12 and 40 days was found but, more interesting, after 12 5 months

the brain weight was significantly decreased However, even this late an oedema cannot be excluded without microscopy

It is of great interest to investigate the long time effects on the neurotransmitters If injury after doses in the therapeutic range would be irreversible it should be of great clinical importance In affective disorders and in some dementia states it has been suggested that these conditions are associated with a functional deficiency of monoamines (SCHILDKRAUT 1965, GOTTFRIES et coll 1969, MENDELS & STINNET 1973) The connection between 5 HT and epileptic manifestations has already been mentioned 5 HIAA and HVA have been widely used to estimate the metabolic state of the parent amine in the CNS No changes were found in the present experiments in 5 HIAA or HVA-concentrations 6 months after irradiation This does not exclude the possibility of a disturbed monoamine metabolism The absence of significant changes of the monoamine metabolites is in contrast to the rather extensive destruction of the parenchyma which was observed This could possibly be due to an increased turnover in the neurons still in function In a short term experiment CATRAVAS & MCHALE found marked changes of the MAO activity after neutron and gamma irradiation Interestingly, the neutron irradiation resulted in a decrease but gamma irradiation was followed by an increase in MAO activity Different results concerning monoamine levels after irradiation could therefore depend on the type of radiation used

Acknowledgement

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SUMMARY

Twenty three rabbits were exposed with ^{60}Co irradiation over the skull Nineteen of the animals received 29 6 Gy over the right hemisphere and 4 animals received 20 Gy over both hemispheres Six months after the exposure the concentrations of 5 hydroxyindolacetic acid (5 HIAA) and homovanillic acid (HVA) in seven different bra ...

ZUSAMMENFASSUNG

Be ...
de ...
... Monaten wurde das Gehirn

biochemisch, lichtmikroskopisch, rasterelektronmikroskopisch und mikroangiographisch untersucht Parenchym- und Gefässveränderungen mit Telangiektasien wurden festgestellt Im Gegensatz zu diesen deutlichen histologischen Veränderungen blieb aber der Gehalt an Monoaminmetaboliten (5-HIAA und HVA) in den verschiedenen Gehirnregionen unverändert

RÉSUMÉ

Vingt trois lapins ont été exposés à l'irradiation du ^{60}Co sur le crane Dix neuf de ces animaux ont reçu 29,6 Gy sur l hémisphere droit et quatre animaux ont reçu 20 Gy sur les deux hémisphères Six mois après l'exposition on a mesuré les concentrations de l acide 5-hydroxyindolacétique (5-HIAA) et de l acide homovanillique (HVA) dans sept régions différentes du cerveau Les auteurs n'ont pas trouvé de différence significative dans les taux de ces métabolites monoaminés par comparaison avec les animaux témoins non irradiés A la différence des modifications biochimiques discrètes, ils ont mis en évidence une destruction parenchymateuse relativement marquée au moyen de la microscopie optique de la microangiographie et de la microscopie électronique par balayage au niveau des vaisseaux qui présentent des télangiectasies, des nécroses fibrinoïdes et des thromboses dues aux effets tardifs de l irradiation

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EVALUATION OF THE CLINICAL USE OF TLD

BENGT INGE RUDÉN

Thermoluminescent dosemeters (TLD) are nowadays widely used in radiation therapy to measure the radiation dose (RUDÉN 1971, SUNTHARALINGAM & MANSFIELD 1971, RUDÉN & NILSSON 1973, LINDSKOUG 1974). Information on the absorbed dose delivered is both a control of the therapy unit and a check that the right parameters are being used for adequate treatment of patients. At Radiumhemmet, SIEVERT (1932) began to use routinely for patient dose measurements small ionization chambers (condensed chambers usually referred to as Bg-chambers), which were entirely separated from the reading instrument.

High quality Bg chambers are not commercially available and it is difficult to maintain and increase their number. Therefore, thermoluminescent dosemeters were introduced for the determination of absorbed doses in routine therapy in 1968. During 1970 the number of clinical measurements amounted to 17 000 of which two thirds were made with TLD and during 1974 the number was 30 000 of which 98 per cent were made with TLD. The purpose of this report is to describe the routine use of TLD for a wide range of dosimetry applications in radiation therapy, the handling of the dosemeters to obtain high accuracy and the usefulness of making patient dose measurements.

Energy dependence of LiF dosemeters

At Radiumhemmet the following facilities are available for treatment: conventional roentgen radiation units (20–200 kV), ^{60}Co units, accelerators for 6 MV and 42 MV roentgen radiation and 5–39 MeV electrons. It is therefore essential to know the response of the different kinds of LiF dosemeters at the various energies used in order to confirm the absorbed doses given to the patients. The primary calibration of the dosemeters was carried out in a ^{60}Co gamma ray beam. The ratio $A_{Co} = T_{Co}/D_{H_2O,Co}$ of the thermoluminescent signal T_{Co} and the absorbed dose in water $D_{H_2O,Co}$ was also used as the primary sensitivity factor for the other radiation qualities, in the

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following denoted by subscript E Since this common practice easily leads to confusion, the *quantities used will be discussed in detail* The relative amount of light detected per unit absorbed dose in the dosemeter will be denoted by L Then

$$T_E = A_{Co}\ D_{H_2O\ Co}\ D_{L\ E}\ L_E/(L_{Co}\ D_{L\ Co}) \quad (1)$$

Subscript L stands for the dosemeter material The relative response k of the dosemeter is defined as the correction factor by *which the ratio A_{Co} should be multiplied* to give the ratio A_E applicable to the actual radiation quality or $A_E = k\ A_{Co}$ Thus

$$k = \frac{D_{L\ E}\ D_{H_2O\ Co}\ L_E}{D_{H_2O\ E}\ D_{L\ Co}\ L_{Co}} \quad (2)$$

The results in Table 1 are expressed *with* the aid of this relative response for high energy electrons and high-energy roentgen radiation (In radiation therapy the term high-energy is often applied to the energy range above about 1 meV) The uncertainties in the results can mainly be attributed to the uncertainty in the determination of absorbed dose in water

The measurements and the theoretical basis of the relative response of the LiF dosemeters to high energy radiation are described by RUDÉN & BENGTSSON (to be published) Determination of the relative response of the LiF dosemeters in the range 20–190 kV was made as follows

The effective photon energies for the different potentials and filtrations were obtained by means of measurements of half value layers in aluminium (20–100 kV) and copper (140–190 kV) and by using mass attenuation coefficients taken from the ICRU Report No 17 (1970)

The exposure measurements at 20–50 kV were made in free air with a PTW soft roentgen ray chamber (W chambers 7241/UI/K) The membrane thickness is 0 03 mg/cm² and the effective volume is 0 3 cm³ The exposure to the dosemeters placed on the surface of a Perspex phantom was calculated by using the backscatter factors published by the Brit J Radiol (Suppl No *11, 1972*) An *FSD of 40* cm and a field size of 15 cm diameter were used Exposure measurements at 100–190 kV were made with a Shonka chamber (*BOAG 1966) The wall thickness is 0 25 mm and the volume 4 36* cm³ The chamber was placed directly on a Perspex phantom and in free air with an FSD of *60* cm and *18* cm × *18* cm *field size Good agreement (within ± 2 per cent)* was obtained between the exposure measurements on the phantom and the results *calculated from the free air chamber measurements with the appropriate backscatter* factors applied (Brit J Radiol Suppl No 11, 1972)

The absorbed *dose in water was calculated by using the results from the exposure* measurements and the appropriate conversion factor (Gy/R) in water (ICRU 17, 1970) During the exposure measurements the LiF dosemeters were placed on the surface of a Perspex phantom The ratio of the thermoluminescent signal and the absorbed dose in water was used as the primary calibration factor at the relevant

Table 1

Measured relative light signal per Gy in water for various kinds of LiF dosemeters for various radiations relative to ^{60}Co gamma radiation

Photon radiation Radiation quality	Total filtration (mm)	0.1 mm Teflon discs*	0.4 0.5 mm Teflon discs*	High sensitivity ribbons**	Teflon rods* Extruded rods**
20 kV	0.1 Al	1.20	0.95	0.78	—
50 kV	1 Al	1.40	1.31	1.36	—
50 kV	2 Al	1.45	1.38	1.43	—
100 kV	1 Al	1.43	1.42	1.45	—
140 kV	4 Al	1.36	1.35	1.38	—
190 kV	0.5 Cu + 1 Al	1.15	1.15	1.17	—
190 kV	Thoraeus	1.12	1.12	1.13	—
^{60}Co	—	1.00	1.00	1.00	1.00
6 MV	—	0.96	0.94	0.97	0.97
42 MV	—	0.96	0.93	0.96	0.97
Electron radiation Energy at the surface (MeV)					
4.3		0.93	0.90	0.90	0.92
7.4		0.93	0.91	0.91	0.94
9.8		0.93	0.91	0.91	0.94
11.6		0.93	0.91	0.91	0.94
14.3		0.94	0.91	0.92	0.95
19.4		0.96	0.92	0.93	0.96
28.2		0.96	0.92	0.94	0.96
39.2		0.98	0.93	0.95	0.97

*Isotope Inc **Harshaw Co

energies to obtain the absorbed dose *in water*. The results expressed according to Eq. 2 for various conventional roentgen ray energies and for various kinds of LiF dosemeters appear in Table 1.

The absorbed dose in water (D_E) expressed in Gy, from the results of TLD measurements at different roentgen ray energies can be calculated as follows

$$D_E = S^{L}_{H_2O} \frac{(\mu_{en}/\varrho)_{H_2O,E}}{(\mu_{en}/\varrho)_{L,E}} \frac{T_E}{A_{Co}} P_E \cdot F_E$$

$S^{L}_{H_2O}$ – the generalized stopping power ratio (^{60}Co) of the the dosemeter material and water at the actual dosemeter size according to BURLIN (1968)

μ_{en}/ϱ – the mass energy absorption coefficient (HUBBELL 1969)

P_E = the correction factor for LET effects on the light yield

F_E = the correction factor for attenuation of the radiation within the dosemeter (calculated).

Table 2

Correction factors for LET and attenuation for 0 13 mm thick LiF teflon discs at various photon energies

Radiation quality (kV)	Total filtration (mm)	Effective photon energy (keV)	Correction factor LET	Correction factor Attenuation
20	0 1 Al	10	1 15	1 10
50	1 Al	17	1 07	1 030
50	2 Al	23	1 05	1 015
100	1 Al	37	1 02	1 005
140	4 Al	51	1 0	1 0
190	0 5 Cu + 1 Al	81	1 0	1 0
190	Thoraeus	97	1 0	1 0

The correction factors for LET effects (P_E) (JAHNERT 1972) and the attenuation (F_E) for 0 13 mm thick LiF teflon discs at the various effective photon energies are given in Table 2 No corrections for LET are needed for ^{60}Co gamma radiation (JAHNERT) Therefore by definition $P_E = 1\ 0$ for ^{60}Co gamma radiation

The ratio of the calculated absorbed dose from TLD and the measured dose from ionisation chamber measurements was between 0 97 and 1 03 This means that within the limits of experimental error the LiF dosemeters have no energy dependence for conventional roentgen ray energies This is in agreement with the results reported by LAW (1973) However, due to the dose inhomogeneity and the attenuation of the thermoluminescent signal in the thicker LiF dosemeters (RUDEN & BENGTSSON), caution should be observed when applying these results in measurements which require high accuracy

Methods

Read-out procedure In routine clinical work the thermoluminescence of the dosemeters was measured with one unit produced by Harshaw (Model 2 000 A and B) and one produced by Teledyne (Model TLD 7100) The most advantageous thermal pretreatment of the LiF dosemeters before they are exposed to ionizing radiation (preannealing) depends appreciably on the type of application and on the desired accuracy This is the case, for instance, in situations where difficulties are encountered in keeping the time between exposure and read-out constant and when continuous exposure during prolonged periods is used This occurs for patient dose measurements as well as in radiation protection measurements The following thermal treatment was used for teflon dosemeters 30 min at 300°C and 24 hours at 80°C preannealing and for Harshaw ribbons and rods 60 min at 400°C and 24 hours at 80°C preannealing Before read out the dosemeters are kept at 80°C for 15 min Separate ovens have been used for various thermal treatments

Table 3

Correction factors to be used for calculation of the given dose from entrance dose measurements for various roentgen ray energies

Radiation quality	Filtration (mm)	Correction factor	
		0 1 mm Teflon disc	0 5 mm Teflon disc
20 kV	0 1 Al	0 83	—
50 kV	1 Al	0 71	—
50 kV	2 Al	0 69	—
100 kV	1 Al	0 70	0 70
140 kV	4 Al	0 74	0 74
190 kV	0 5 Cu + 1 Al	0 87	0 87
190 kV	Thoreaus	0 89	0 89

In physical measurements which require high accuracy and where it is possible to cancel out the effect of fading, the heating during the read out procedure was used as the only method for preannealing (CARLSSON et coll 1968) In such measurements the time interval between the irradiation and the read-out of a dosemeter was kept the same in both calibration and experiment

Irrespectively of what kind of preannealing method was used all the dosemeters were retained in the read out apparatus for 1 min after the integration was completed in order to provide identical cooling-cycles

Calibration of the thermoluminescence dosemeters Separate groups of dosemeters, each containing 25, were used Calibration factors in Gy/digit were assigned to the individual dosemeters after the calibration procedure In addition, five dosemeters were used for calibration purposes in connection with every measurement occasion The mean value of the change in the calibration factor found for these 5 dosemeters was applied to all the other dosemeters included in the same group Such a procedure was made possible by running all dosemeters within the group through exactly the same heating and cooling procedure (MÅRTENSSON 1969) It was observed that when a new dosemeter was employed, its sensitivity increased markedly during the first applications All the dosemeters must be read out and irradiated with the same geometry to obtain good reproducibility, that means that the dosemeters must not be turned in any way with respect to one another The dosemeters are marked and the practice is that the unmarked side should always be turned to the treatment apparatus during the irradiation and to the PM tube during the read out

In vivo dosimetry

Each of the many steps in the planning and execution of irradiation of patients may contribute significantly to the uncertainty in the absorbed dose given to the patient

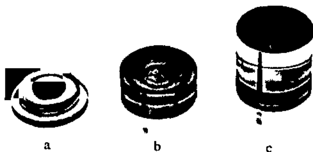


Fig 1 Perspex dosemeter holders (diameter 20 mm) for patient dose measurements a) Bottom of a holder containing two LiF teflon dosemeters b) Holder used for ^{60}Co gamma radiation c) Holder used for 6 and 42 MV roentgen radiation

Human mistakes and malfunction of the therapy units may cause considerable deviations from the planned treatment An ultimate control of the given absorbed dose is only possible by using in vivo dosimetry Another important application of in vivo dosimetry is to estimate the absorbed dose contribution to organs such as the eyes or gonads in which relatively small radiation doses might be particularly undesirable (RUDEN, RUDÉN & NILSSON)

In vivo dose measurements consist of determinations of entrance dose, exit dose and intracavitary dose measurements At Radiumhemmet, different types of dosemeters are used for each of these types of measurement LINDSKOUG used an automatic read-out apparatus which only reads rods and these were used for all kinds of patient dose measurements

Entrance dose measurements, previously by means of Bg-chambers, nowadays by TLD, are mainly performed for checking output, performance of the therapy unit and the accuracy of the setting-up of the patient, but sometimes also in order to determine the dose distribution within irregularly shaped beams

Orthovoltage roentgen radiation In connection with external orthovoltage roentgen ray therapy 0 1 mm thick LiF teflon discs (diameter 12 7 mm) are used at 20–50 kV *and 0 5 mm thick LiF teflon discs (diameter 8 mm) at 100–190 kV Since the dose*meters are calibrated using ^{60}Co gamma radiation, correction factors must be applied to obtain the given dose in Gy in water These correction factors appear in Table 3 The factors have been calculated from the results presented in Table 1

^{60}Co gamma and high energy roentgen radiation When the entrance dose is to be determined in external gamma and high energy roentgen ray therapy, two LiF-teflon discs (diameter 8 mm, thickness 0 5 mm) are placed in specially designed build up caps (Fig 1) The dosemeter assembly is attached to the body surface It must be observed that when the build-up cap is placed on the skin, the skin-sparing effect is considerably reduced under the dosemeter assembly By changing the position of the build up cap between sessions, this effect is minimized The thickness of the build-up layer is 4 mm for the ^{60}Co beam and 15 mm for the 6 MV and 42 MV beams

Table 4

Correction factors to obtain the maximum absorbed dose for various beam sizes and SSD for 42 MV roentgen radiation when using build up cap according to Fig 1 c

	SSD										
	100 cm										120 cm
Beam cm cm	5×5	6×6	7×7	8×8	9×9	10×10	11×11	12×12	13×13	15×15	16×16 20×20
Correction factor	1 28	1 26	1 25	1.22	1.20	1 18	1 16	1 14	1 13	1 11	1 25

The build up thickness of 15 mm is too small, however, when the given dose from 42 MV radiation is to be determined A correction factor, which has been determined by means of measurements, must therefore be applied The correction factors for various beam sizes and SSD used at the Siemens 42 MeV betatron, are given i Table 4 The same beam flattening filter is used for all beam sizes (filter 2) These corrections factors have also been confirmed through calculations using depth dose curves and the energy dependence of the dosemeters

High energy electrons When the given dose is to be determined by entrance dose measurement in electron therapy, a build up cap is not used However, the relation ship between the surface dose thereby determined and the dose at the maximum varies with the energy of the electrons and the scattering foil used for a particular beam size In order to get the absorbed dose at the maximum, correction factors must be applied These factors are dependent on the energy and the kind of scattering foil used and they have been determined by means of measurements The correction factors for tubes from 6 cm × 8 cm to 20 cm × 20 cm (including correction both for the energy dependence of the LiF teflon dosemeters and that the dosemeters are at the surface) used at the Siemens 42 MeV betatron, appear in Table 5

Entrance measurements of the absorbed dose with TLD is not only a control of the given dose but also an aid in determining the entrance dose at different points in irradiations with large irregular beams over an area where the body contour may also be irregular, e g with the mantle technique (Fig 2) and the inverted Y technique

It is sometimes important to measure the absorbed dose to organs *outside the primary beam and particularly* under beam shaping blocks In particular organs (eyes gonads) a relatively small radiation dose might be particularly undesirable In these measurements on patients individually calibrated, high sensitivity LiF ribbons (3 2 mm × 3 2 mm × 0 9 mm) are used for the determination of absorbed doses which represent only minor fractions of the therapeutic dose

Exit dose measurements are most commonly made for the purpose of checking calculations of the absorbed dose to deep-seated internal structures *The exit dose*

Table 5

Correction factors to obtain the maximum absorbed dose at different electron energies

Energy at the surface (MeV)	5	7 5	10	10	12 5	15	20	30	39
Scattering foil (number)	2	2	3	4	4	4	5	5	5
Correction factor	1 30	1 35	1 25	1 18	1 18	1 12	1 12	1 11	1 10

method is applicable even for calculation of the absorbed dose to the tumour in the irradiation (SUNDBOM 1965), e g with irregularly shaped beams

No individual treatment plans are drawn up for patients treated with mantle or inverted Y-technique When these types of irradiation were started, exit dose measurements were made at various points (Fig 3) On patients treated for carcinoma of the oesophagus, exit dose measurements are made at different points in the caudal cranial direction of the beam This technique is used to measure the variation of the absorbed dose along the length of the oesophagus The dosemeters used for the exit dose measurements are placed in a perspex cap to ensure adequate scattering conditions

Intracavitary dose measurements Since the introduction of condenser chambers, (SIEVERT) dose measurements have been carried out in readily accessible body cavities such as the mouth, vagina, rectum This technique has also been successfully applied in the oesophagus (LIDÉN 1948, DAHL & VIKTERLOF 1960) and also in the bladder (DAHL & VIKTERLÖF) Thermoluminescent dosemeters have now become available in sizes and shapes that make them suitable for dose determination in pelvic veins (TJERNBERG et coll 1968, JOHANSSON et coll 1969, JOELSSON & BACKSTROM 1970)

Measurements in veins and in the oesophagus In an investigation performed as a cooperative project by the departments of Gynaecology and Clinical Radiation Physics at Radiumhemmet and the Unite de Radiophysique, Institut Gustave Roussy in Paris, the correspondence was tested between computer calculated doses in various parts of the pelvis and the doses in the same sites measured with LiF dosemeters (JOELSSON et coll) LiF rods (diameter 1 mm, 6 mm long) loaded into presterilized teflon catheters were introduced into the external and common iliac veins by a technique commonly used for venous catheterization Lead spacers had been placed between the dosemeters to allow, after phlebography, a precise roentgenologic determination of the location of each numbered LiF rod in relation to the pelvis The dosemeters were left in situ during the whole course of treatment

Intracavitary measurements with LiF rods have been made in the oesophagus of patients treated with the mantle technique and in external and common iliac veins in treatments with the inverted Y-technique

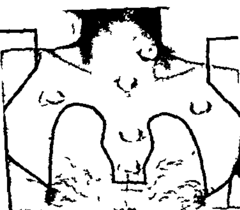


Fig 2

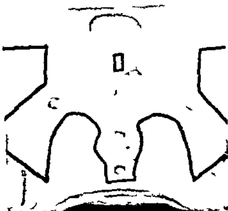


Fig 3

Fig 2 Clinical set up designed to determine entrance doses for a mantle field treatment

Fig 3 Clinical set up designed to determine exit doses for a mantle field treatment The dosemeters are applied in the plastic shell which is used for patient fixation

Certain cases of oesophageal carcinoma are preoperatively irradiated by a three beam technique two posterior oblique beams and one anterior beam In order to optimize the treatment of the patients, an individual dose plan is made The isodose distribution from these 3 beams is calculated by applying a correction for lung tissue using an isodose shift method (l/2 isodose shift method, SUNDBOM) In order to check the tumour dose calculated according to the plan the absorbed dose has been measured in the oesophagus 16 times in 12 patients irradiated with ^{60}Co For these intracavitary measurements the dosemeters used were extruded LiF rods inserted in a teflon catheter The use of lead spacers between the LiF rods made it possible to determine the anatomic location of each dosemeter in the oesophagus The lead spacers give the dosemeters about +3 per cent higher value for ^{60}Co gamma radiation than if plastic markers are placed between the dosemeters

Phantom measurements Measurements have also been made with extruded LiF rods in the oesophagus in an anatomic Temex phantom The air space in this phantom, simulating the lungs was filled with saw dust with a density of 0 25 g/cm^3 This is the material that was stated by DAHL & VIKTERLÖF and SUNDBOM to be radiation equivalent to an air filled lung The Temex phantom was irradiated with a three beam technique identical to that used for the treatment of carcinoma of the oesophagus

Frequency of in vivo dose measurements

The entrance dose is measured on patients treated with orthovoltage units (90–190 kV) ^{60}Co units and the 6 MV linear accelerator for every beam during the first 2 treatments and then repeated at each beam when the tumour dose is 20, 40 and

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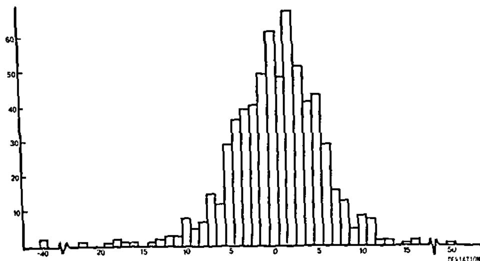


Fig. 5 Deviation (in per cent) during one year of the measured absorbed dose from the prescribed absorbed dose on patients treated on the 6 MV linear accelerator with open beam Mean +0 6, SD ±4 8 Total number 619 measurements

Table 6 summarizes the results from entrance dose measurements on various treatment units The table gives the mean value of the difference between measured and prescribed absorbed dose and the standard deviation of these differences for all entrance dose measurements during one month on all the various treatment units

Fig 6 illustrates a histogram of the deviation from the prescribed absorbed dose on patients treated with an irregularly shaped beam where lead blocks were placed in the corners and in the centre of the beam The mean is +4 4 per cent, indicating a systematic error An investigation demonstrated that too high a correction factor

Table 6

The mean value of the difference between measured and prescribed absorbed dose and the standard deviation of these differences for all entrance dose measurements during one month on all the various treatment units

Treatment unit	Mean (per cent)		Standard deviation (per cent)	
	Open beam	With wedge	Open beam	With wedge
Cobalt	−1 5	1 0	±4 5	±6 3
Linear acc	+0 6	+0 3	±4 6	±6 1
Betatron roentgen rays	−2 6	—	±4 4	—
Betatron electrons	+1 9	—	±5 8	—

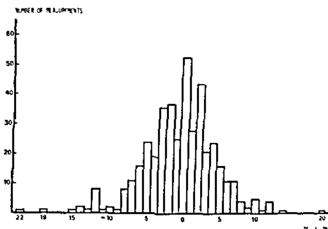


Fig 4 Deviation (in per cent) during one year of the measured absorbed dose from the prescribed absorbed dose on patients treated on the 6 MV linear accelerator with wedge filter in the beam Mean +0 4, SD ±4 7 Total number 417 measurements

60 Gy For patients treated with an orthovoltage unit (20–50 kV) and with electrons and 42 MV irradiation at the 42 MeV betatron, the entrance dose is nowadays measured at every irradiation

Exit dose measurements are made on patients treated for carcinoma of the oesophagus at various points in the caudal-cranial direction of the beam and in the lungs for every beam during the first 2 treatments and then repeated for each beam 2 or 3 times throughout the whole treatment course

Intracavitary measurements are sometimes discomfortable for the patient but when possible two measurements are made during the whole course for patients treated for carcinoma of the oesophagus

When a new therapeutic technique is introduced, intracavitary measurements are sometimes made as a control of the dose planning procedure

If the eyes are close to the primary beam or under beam shaping blocks, measurements are made at every treatment

The absorbed dose to the gonads is measured for every beam in the first irradiation and then repeated when the tumour dose is 20 Gy on patients treated with the inverted Y technique

Results

Long-term stability of the measuring technique The mean values from day to day of all entrance dose measurements on the different accelerators give an indication of a sudden change or the long term drift effect in the dosimetry system Figs 4 and 5 illustrate histograms of the deviation during one year from the prescribed absorbed dose with TLD on patients treated at the linear accelerator with beams with and without a wedge filter

Each dosemeter assembly for entrance dose measurements contains two LiF teflon discs (cf Fig 1) The difference in the readings between the two detectors used in the same dosemeter assembly was less than 5 per cent in 93 per cent of all entrance dose measurements during one year The precision of one individual reading has been found to be within ±2 per cent (1 s)

Table 8

Anatomic regions and corresponding beam sizes for calculating the absorbed dose in the centre of the patient in treatments with mantle and inverted Y-technique

Mantle technique		Inverted Y technique	
Area	Beam size (cm × cm)	Area	Beam size (cm × cm)
Neck	5*5	Sternum	12 × 12
Axilla, supracl fossa	15 × 15	Centre	12 × 12
Centre	15 × 15		
Mediastinum	10 × 10	Inguinal	8 × 8

by a factor 3 in a small area in the centre of the beam These mistakes indicated that a more advanced interlock system must be built into the betatron to avoid wrong settings and that the entrance dose should possibly be measured for every treatment. In 1974 the betatron was fitted with an interlock system (HUZELL & ISRAELSSON 1975) The fact that the entrance dose has since been measured with TLD at every irradiation has probably also minimized the frequency of errors At present less than 5 per cent of the treatments indicate a fault outside the action level in the entrance dose measurements These faults in the entrance doses can easily be compensated for since the measurements have given the error

Intracavitary and exit dose The evaluation of all exit and intracavitary measurements on patients who have been treated with mantle or inverted Y-technique had led to the conclusion that different equivalent beam sizes must be used to calculate the dose in the centre of the patient in different anatomic regions (Table 8) To calculate the absorbed dose in the centre of different regions the depth dose curve (for SSD 150 cm) corresponding to the field sizes illustrated in Table 8 has to be used Measurements made in a Temex phantom have confirmed the usefulness of these equivalent beam sizes to calculate the absorbed dose in the centre of the patient within an accuracy of ± 5 per cent

In some patients treated for oesophageal carcinoma, the absorbed dose was found to vary as much as 20 per cent along the length of the oesophagus The difference between measured absorbed dose and the calculated absorbed dose (corrected for lung tissue) had a mean value of +8 per cent (range −6 to +16 per cent) The exit dose measurements gave the same indication The measured absorbed dose was corrected for the influence of the lead spacers between the dosemeters The agreement between two intracavitary measurements for the same patient was within ± 3 per cent

The results from the measurements in the Temex phantom agreed well (within ± 3 per cent) between calculated and measured absorbed dose in the oesophagus The agreement between the absorbed dose in the oesophagus calculated from exit dose measurements on the phantom and the given dose was within ± 6 per cent

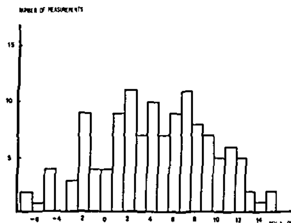


Fig 6 Deviation (in per cent) of the measured absorbed dose from the prescribed absorbed dose on patients treated on the

had been used for the attenuation of the radiation in the Perspex sheet on which the lead blocks were placed A change had been made from a thicker to a thinner sheet without giving notice to the planning department

The limits of the dosemeter deviation from the prescribed dose that have been found to be realistic action levels appear in Table 7 If the limits are exceeded a control of the treatment parameters must be made If the cause of deviation cannot be found a new measurement of the entrance dose must be performed at the next irradiation

Entrance dose At the ^{60}Co units and the 6 MV linear accelerator, between 10 and 20 per cent of the entrance dose measurements exceed the action level and in about 4 per cent some errors regarding treatment parameters exist In the other cases where the reason was not found, the deviation from the prescribed absorbed dose was in no case larger than ± 12 per cent

The entrance dose measurements on patients treated with the 42 MeV betatron during the first years after the installation, indicated that some mistakes in the settings of the treatment parameters on the apparatus could occasionally cause severe overdosage Two examples are given here On one occasion several patients were treated *with 39 MeV electrons instead of* 10–15 MeV electrons This fault gave rise to an overdosage of about 80 per cent Some patients were treated with 42 MV roentgen rays without a beam flattening filter This gave an absorbed dose which was too high

Table 7

Tolerable deviation from prescribed absorbed dose to a patient

Radiation quality	Tolerable deviation (per cent)
20–200 kV	± 10
^{60}Co 6 MV roentgen rays	$+5$ ($+7$ with wedge)
42 MV roentgen rays	± 5
Electrons	$+7$

2 Malfunction of shutter on a ^{60}Co unit
3 Contamination of a ^{60}Co source with a short lived radionuclide

The mistakes listed in point 1 are not unusual and any of these occurred in about 3 to 4 per cent of the treatments

Conclusion

The in vivo dose measurements on patients with TLD have shown the importance of these kinds of measurements for increasing the accuracy of the treatments of patients These dosemeters are suitable for their purpose and easy to handle, for example in intracavitary measurements in the oesophagus and in veins, surface dose measurements entrance and exit dose measurements at a number of points in irregular fields measurements of the dose distribution in the electron field on patients treated for carcinoma of the breast where the curvature of the chest varies from one patient to another, checking of absorbed doses in critical regions near the target volume and below lead shields and for radiation protection measurements In order to be sure that the patients are always given the correct absorbed dose, patient dose measurements must be made for every treatment The evaluation of the entrance dose measurements on patients treated with irregularly shaped beams, where lead blocks were placed inside the beam, shows the usefulness of patient dose measurements to find unexpected errors in the treatment of patients It was concluded from the patient dose measurements that it was most important to build in an interlock system at the 42 MeV betatron to increase the accuracy of the treatments

A comparison between the standard deviation in Table 6 (e g 4 5 per cent for open beams with ^{60}Co radiation) with the reproducibility of the two detectors in the dosemeter assembly ($s - \pm 1$ 5 per cent) indicates that only a minor contribution to the overall variance is due to the detectors

The conclusion from the measurements of the absorbed dose in the oesophagus was that a standard correction factor for all patients to compensate for transmission through lung tissue (the 1/2 shift method) used in the dose planning for each patient, could not be consistently applied If the size of the lung is not drawn with sufficient accuracy in the plan this may contribute to an error in the calculated absorbed dose Measurements of the actual absorbed dose is therefore necessary in each case To avoid unnecessary patient discomfort and because of the possibility of perforating a diseased oesophagus, exit or transit dose measurement would appear to be a good complement to or alternative for the determination of the absorbed dose in the oesophagus even if these methods give less accuracy than a direct measurement in the oesophagus Use of the 1/2 isodose shift method can in some cases result in an inaccuracy of about +15 per cent in the tumour dose With no correction for the lungs the absorbed dose in the oesophagus will be about 25 per cent greater than that calculated (JACOBSON & KNAUER 1956) Use of a standard correction factor of 1 20

Discussion

Uncertainties and errors in clinical dosimetry are two distinct concepts, the former refer to the chain of measurements leading to the delivery of a prescribed absorbed dose to a patient, mistakes caused by staff are errors

Concerning the uncertainty, LOEVINGER & LOFTUS (1975) have set up a model which aims to include every link in the dosimetry chain from the national standardizing laboratory to the delivery within a hospital of an absorbed dose to a point in a phantom They estimated the cumulative overall uncertainty to 5 1 per cent for the lowest acceptable model and 2 3 per cent for the model representing the best level of current practice

The second stage of the clinical dosimetry procedure, in which the dose is delivered to a target volume in a patient, rather than to a uniform phantom, introduces a further series of uncertainties which are difficult to assess Uncertainties associated with the patient are discussed in the ICRU report Clinical dosimetry (1963)

A control on the precision of the whole chain including unforeseen and long-term drift effects in a dosimetry system, is obtained from the entrance dose measurements on patients These are therefore important in providing a check on the uncertainty regarding the precision but not on the accuracy

Every week a control of the treatment chart (scale division/Gy) is made on the accelerators with an ionization chamber If this measurement shows a deviation of more than ± 3 per cent from the treatment chart, a correction is made in the build-in dosimetry system The entrance dose measurements on patients with TLD on each of the accelerators will give an indication as to whether and when it is necessary to make a correction in the build-in dosimetry system An unforeseen change in dosemeter systems at the accelerators has only occurred four times since their installation seven years ago

In recent years a number of reports have appeared, assessing the incidence and significance of mistakes in the various stages of clinical dosimetry Data have been obtained from KARTHA et coll (1973, 1975), CHUNG-BIN et coll (1975) and SUTHERLAND (1973)

A frequency of errors of about 4 per cent per year for mistakes leading to an error of 5 per cent or more in the final tumour dose was reported by SUTHERLAND KARTHA et coll found an incidence of 10 per cent in mistakes of arithmetic nature and in the [illegible]

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Entrance dose measurements on patients at Radiumhemmet have shown that the following faults have occurred

1 Mistakes in the setting up (a) wedge filter, (b) energy, (c) scattering foil, (d) change of beam flattening filter, (e) treatment time or scale setting, (f) distance, and (g) field sizes

Dosimetrie-Anwendungen in der Strahlentherapie, die Handhabung der Dosimeter, um eine hohe Genauigkeit zu erhalten, und die Nutzlichkeit von Dosismessungen am Patienten werden beschrieben

RÉSUMÉ

L'auteur a mesure l emission relative de lumière par Gy dans l'eau pour le rayonnement roentgen ordinaire (20–190 kV), pour le rayonnement roentgen de haute énergie (6 et 42 MV) et pour les électrons entre 2,2 et 34,5 MeV par rapport au rayonnement gamma du ^{60}Co pour differents types de dosimetres LiF L'auteur decrit l'utilisation pratique des dosimètres au LiF pour un large domaine d'application dosimétrique dans le traitement par les radiations, la façon d utiliser les dosimètres pour obtenir une haute précision et l'utilité de faire des mesures de doses sur le patient

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and R[illegible]

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can result in an accuracy of 10 per cent in the tumour dose (WRIGHT & STROCKBINE 1974)

The measurements of the dose contribution to organs in which even relatively small radiation doses might be particularly undesirable have been useful, these measurements gave, among other things, an indication as to whether the lead shield was in right position and whether it gave sufficient protection These measurements on patients treated with the inverted Y-technique have demonstrated the necessity of increasing the shielding over the gonads

A number of irradiations are given with low kilovoltage The apparatus used at Radiumhemmet for these treatments has no interlock system despite the fact that with certain potential and filter combinations the exposure rate is extremely high This means that the treatment times are sometimes as short as a few seconds It is advisable to make TLD measurements during these treatments to verify the given dose

One disadvantage of using TLD for patient dose measurements is that an unavoidable time delay exists between the irradiation and the presentation of the results from the measurements With the number of the staff it is impossible to increase the number of TLD measurements at Radiumhemmet Attempts are being made to measure the entrance dose with solid state detectors connected to an integrating instrument which gives an immediate indication of the results (BÅRYD 1975) This will not reduce the value of TLD for more advanced patient dose measurements

Acknowledgements

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SUMMARY

The relative light output per Gy in water for conventional roentgen radiation (20 190 kV) high energy roentgen radiation (6 and 42 MV) and electrons between 2 2 and 34 5 MeV relative to ^{60}Co gamma radiation is reported for different kinds of LiF dosemeters The routine use of LiF dosemeters for a wide range of dosimetry applications in radiation therapy, the handling of the dosemeters to obtain high accuracy and the usefulness of making patient dose measurements are described

ZUSAMMENFASSUNG

Die relative Lichtausbeute per Gy in Wasser fur konventionelle Rontgenstrahlung (20–190 kV), hochenergetische Rontgenstrahlung (6 und 42 MV) und Elektronen zwischen 2,2 und 34,5 MeV relativ zur ^{60}Co Gammastrahlung fur verschiedene Arten von LiF Dosimetern wird berichtet Der Routinegebrauch von LiF Dosimetern fur einen weiten Bereich von

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BLURRING QUALITY IN SPIRAL TOMOGRAPHY

G HARDING and M J DAY

In a recent article, ÅSTRAND & REICHMANN (1974) drew attention to the important fact that tomographic blurring has a qualitative, as well as a quantitative, aspect Illustrating their ideas by reference to circular tomography, they were able to show that a great improvement in blurring quality could be obtained by superimposing several tomographic exposures, each performed using a circular movement of different radius Since such a movement approximates to a spiral, this conclusion was taken to indicate the possibility of obtaining blurring of good quality using a spiral tomographic movement

It was apparent from the experimental evidence presented by ÅSTRAND & REICHMANN that blurring quality is an important general factor to be considered in tomography, in spite of its apparent neglect in the past in favour of the quantity of blurring The purpose of the present communication is therefore *to reconsider* the question of blurring in spiral tomography, but from a rather different standpoint to that of ÅSTRAND & REICHMANN

Blurring quantity and quality in tomography

In [illegible] achieving this purpose have been proposed, of which a few have been accepted into clinical use In attempting to compare the character of the blurring offered by various types of tomographic movement, it is

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The transfer function approach, which will be developed below, allows objective analysis of both quantity and quality of blurring, and provides a method for con trolled modification of the quality of blurring associated with different types of tomographic movement

The transfer function is, of course, merely one of several ways of approaching the problem of image blurring in tomography Other ways of dealing with this problem have been discussed by MATTSSON (1972), and would naturally be expected to yield similar conclusions In this context it is interesting to see how MATTSSON s criticisms of various types of tomographic movement are endorsed by the transfer function approach, in spite of the apparent dissimilarity of the two standpoints The transfer function is adopted here since it seems an appropriate and powerful way of dealing with the problem of blurring quality in tomography

The point spread function and transfer function in tomography

One of the most natural and useful measures of blurring in any type of imaging system is the Point Spread Function (PSF) GOODMAN (1968) who terms the PSF the impulse response function', has given a good account of the application of the PSF to several imaging problems in optics In the optical case, the PSF corresponds to the image of a point source of light and depends both on the positions of the object and its image In radiography, it is defined in an entirely analogous way, as the image of a point object (e g a small pinhole in a thin lead sheet) formed by the radiation system Although the PSF is well established in optics (GOODMAN) and radiography (ROSSMANN 1969) it has apparently been little used in tomography

By way of example, consider the case of circular tomography The PSF (the distribution of radiation flux across the film) is confined to a point if the object is located in the tomographic plane but for other object positions forms a circular ring whose radius increases approximately linearly with the perpendicular displacement of the object from the tomographic plane

Under the usual, and essentially valid assumptions (ROSSMANN), the tomographic image of an out of focus section can be described as the spatial convolution of an ordinary radiographic image of that section with the PSF appropriate to that section The operation of convolving two functions describes in mathematical terms the smearing out of the one *by the other* In the present case, the interest is focused on the blurring of the sharp radiographic image by the PSF arising from the tomographic movement Detail in the object section whose dimensions are large compared to the point spread coefficient will *emerge* almost unmodified from the convolving operation but small structures will become so smeared out as to be unobservable

Additional insight into the blurring operation can generally be gained by considering it in terms of its effect on the *sinusoidal* components into which any object may be analysed i e its spatial frequency spectrum It is a standard result that blurring can be described in an entirely equivalent manner to that above, as a frequency

clear that two quite distinct, though related, considerations are involved Using the terminology of ÅSTRAND & REICHMANN, these are the quantity and quality of blurring

Blurring quantity The images of overlying structures must, as far as is consistent with clear depiction of the object layer, be blurred-out from the tomographic image This requirement usually provides the main criterion by which different types of tomographic equipment are compared Given equally satisfactory demonstration of the tomographic section, the optimum system is the one which gives maximal blurring of—and therefore minimal visual interference from—non-tomographic sections

It is not, in practice, possible or indeed advantageous to increase the blurring out of unwanted layers indefinitely, since clear perception of the structures of interest, among the blurred images of overlying layers, requires that the tomographic layer must appear not only in reasonably sharp focus but also with adequate contrast This means that, loosely stated, a certain minimum 'depth of focus' is necessary, its actual value depending both on the structure under examination and the nature of the supposed defect Since the depth of focus is related to the angular range of the tomographic movements, a limit is thereby placed on the maximum acceptable angular range, and hence on the blurring-out of unwanted images

Blurring quality Since it is not practicable to eliminate completely the images of non-tomographic layers, it is important that the blurring process should not result in misleading residual images For example, the blurring should be free from such artefacts as spurious contours, contrast reversals etc , especially for structures just outside the tomographic layer, whose images are only slightly blurred

In addition to these fundamental criteria, the requirement that the tomographic section itself should be rendered in sharp focus imposes limitations on the size of the source, on the inaccuracies in the mechanical movements and on any other causes of unsharpness originating in the tomographic system Such defects, while often of considerable technical importance, do not alter the principles of tomographic blurring and they are therefore assumed to be negligible

Specification of blurring quantity and quality In order that the quality of blurring obtained in different types of tomographic system may be discussed in more nearly comparable terms it is useful to refer to a single quantitative specification of the quantity of blurring Although there are obviously dangers involved in the use of a single numerical quantity, it has been proposed (DAY 1976) that a reasonable and consistent parameter is provided by a 'point spread coefficient' analogous to the standard deviation in statistics

On the other hand, except for some empirical observations, no precise criteria have been presented so far by which the quality of blurring may be specified Indeed since blurring quality must ultimately be assessed visually, it is likely that such criteria would involve physiological as well as physical considerations

The transfer function approach, which will be developed below, allows objective analysis of both quantity and quality of blurring, and provides a method for controlled modification of the quality of blurring associated with different types of tomographic movement

The transfer function is, of course, merely one of several ways of approaching the problem of image blurring in tomography Other ways of dealing with this problem have been discussed by MATTSSON (1972), and would naturally be expected to yield similar conclusions In this context it is interesting to see how MATTSSON's criticisms of various types of tomographic movement are endorsed by the transfer function approach, in spite of the apparent dissimilarity of the two standpoints The transfer function is adopted here since it seems an appropriate and powerful way of dealing with the problem of blurring quality in tomography

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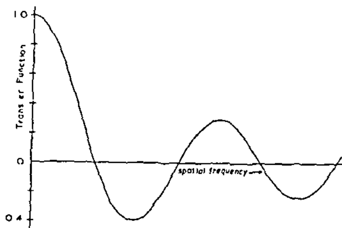


Fig 1 Theoretical transfer function for a circular tomographic system The spatial frequency axis may be scaled to all object sections as explained in the text A sinusoidal object of spatial frequency 0 25 mm $^{-1}$ (wavelength 4 mm) imaged at 50 mm out of the tomographic plane using a 12° circular movement, would correspond to a frequency value near the fourth node of the transfer function to the far right of the figure

dependent modification of the object spectrum (ROSSMANN) The modification factor is termed the transfer function, and represents the proportion of each frequency component present in the object which is transferred to the image by the imaging system It is usually normalised to the value unity for zero frequency i e for a uniformly featureless object

In an ideal system, in which the only cause of unsharpness is the tomographic blurring, the transfer function for the tomographic plane is unity at all spatial frequencies This implies that detail inside the tomographic plane is perfectly imaged onto the recording film For low fequency components just outside the tomographic plane, the transfer function would be expected to be still appreciable, since such components correspond to structures of large spatial extent, which remain almost unaffected by the blurring process Conversely the transfer function for high frequency components outside the tomographic section, corresponding to small overlying structures, would be expected to be small, since such structures are virtually eliminated from the tomographic image It will be seen that these remarks do indeed hold for the transfer functions encountered in tomography It may also occur that the phase of the image of an out-of-focus frequency component differs from the phase of the object component, corresponding to a shift of the sinusoidal image away from its true position If the PSF is symmetrical (e g linear or circular tomography) the phase shift may take only the values of zero or half a wavelength, for asymmetric functions such as the spiral, however, any value of phase difference may occur

It has been seen that tomographic blurring can be described with equal validity in terms of the PSF or the transfer function In fact there is a close relationship between these two functions, for they are simply Fourier transforms of one another (ROSSMANN) Therefore, knowing the form of the PSF (which in an ideal tomographic system is simply the shape of the source/film movement) and the exposure delivered to each point on the PSF, it is possible to derive the transfer function without any other information

The transfer function in circular tomography In circular tomography the PSF is an

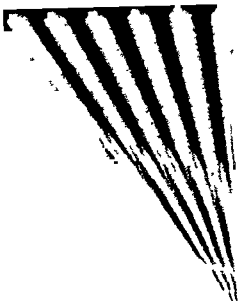


Fig 2 Tomogram of a fan like test object located 20 mm above the tomographic plane of a circular system of 12 radius movement Regions of poor contrast and contrast reversal correspond to the nodes and [illegible] due to harmonics present in the spatial spectrum of the test object owing to its square-wave rather than sinusoidal form

annulus whose radius is directly proportional to displacement from the tomographic plane The transfer function can be derived analytically in this case and is a zeroth order Bessel function $J_0(\rho R)$ (see Appendix) The variable R represents the radius of the annulus and ρ represents the spatial frequency This function is drawn out in Fig 1 The transfer function has the same form as Fig 1 for all possible object sections at large values of R (large distances from the tomographic plane) the frequency scale is expanded implying that high frequency components become strongly attenuated whereas at low values of R (close to the tomographic plane) the frequency scale is contracted so that high frequency components are imaged relatively unmodified This scaling property of the circular transfer function applies to all types of tomography

A further important property of the function $J_0(\rho R)$ is that it contains negative portions after alternate nodes of the function In these regions of spatial frequency, contrast reversal occurs i e a sinusoidal object is imaged with light and dark areas interchanged because the image has been shifted by half a wavelength relative to its true position

This behaviour of the transfer function is illustrated experimentally in Fig 2 which is a circular tomogram of a fan like test object positioned some distance outside the tomographic section (The true form of the object can be gauged from Fig 4) The test object was constructed to have increasing spatial frequency down the figure, but predominantly one frequency across the figure There is good contrast

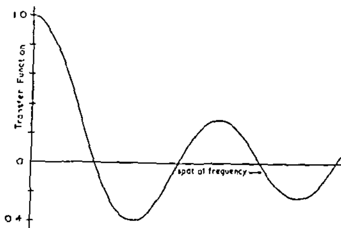


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Fig. 4 Tomogram of the test object used for Fig 2 obtained with a triple-circle movement, but otherwise under identical conditions to those of Fig. 2

concentric circles of radii 0 5, 1 0 and 1 5 (arbitrary units) assuming that the same exposure is delivered in each circular orbit Fig 4 is a tomogram of the test object used for Fig 2, obtained using the triple circle movement a marked improvement in the form of the image is evident, such defects as remain resulting from the very high spatial frequencies present in the test object at the edges of the spokes Since tomography is inappropriate for imaging very fine detail, such frequencies would be unimportant in practice However, if the number of circles in the PSF was increased, it would of course be possible to achieve better correction of the transfer function up to higher spatial frequencies

Clinical example of three circle tomography It is difficult to make immediate clinical tests of the three-circle method, because of the time required to make mechanical adjustments to the radius of the tomographic movement However, three-circle tomograms have been taken of a skull phantom, chosen primarily because it includes complex anatomic structures, and the results appear in Fig 5

Fig 5 a–c are single circle tomograms performed at successively large radii, and hence with increasing quantity of blurring they each contain various artefacts associated with circular tomography, such as double contours and other spurious detail Fig 5 d is a triple-circle tomogram, with practically the same quantity of blurring as Fig 5 b, yet it gives the subjective impression of providing more effective

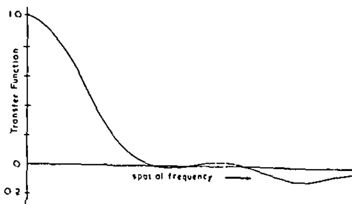


Fig 3 Transfer function calculated for a tomographic movement comprising three concentric circles of radii 0 5 1 0 and 1 5 (arbitrary units) The exposure assumed for each circular orbit is the same The spatial frequency scale is identical to that of Fig 1 if the single circle assumed there is taken to have unit radius

between the light and dark bands of the image of the test object at the top of the figure, implying a high transfer function, but the contrast generally deteriorates towards the higher frequencies lower down, showing a diminishing transfer function At certain frequencies near regions of low contrast, the light and dark bands seem to shift along by one bar of the image These shifts correspond to the contrast reversals mentioned above

Defects in the transfer function It is well-known that a transfer function having the characteristics illustrated in Fig 1 leads to gross aberrations in the form of the transferred image, of which the most serious is the phenomenon of 'ringing' (This is the appearance of parallel light and dark bands around any sharp edge, and is analogous to the spurious contours and contrast reversals which occur in tomographic images) As noted by WOLTON & REDMAN (1972) in connection with optical images, phase changes of 180° in the transfer function can lead to acute ringing Ringing is also encountered in the transmission of video information, where it can be caused not only by the presence of phase distortions, but also by the use of a transfer function having a sharp cut off at an upper frequency limit to the passband Some interesting examples of the video image aberrations which result from transfer functions suffering from various defects have been presented by AMOS & BIRKINSHAW (1965)

Correction of transfer function defects using multiple circles In principle, it should be possible to eliminate blurring aberrations by modifying the PSF in such a way that the corresponding transfer function shows no phase distortions or sharp cut-off points This was, in fact, the approach used by HARDING & DAY (1975) to remedy the blurring defects in linear tomography In circular tomography (including transaxial tomography) as it stands, it seems impossible to modify the PSF in any useful way

However, by superimposing several tomographic exposures, using circular movements of different diameters, it is indeed possible to achieve an improved transfer function, at least over a limited range of spatial frequencies Fig 3 shows the theoretical transfer function calculated from a PSF which is the superposition of three



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Fig 5 Circular tomograms of a skull phantom The tomographic plane is parallel to the base of the skull and about 20 mm below it The exposure in each figure is 900 mAs at 70 kV a) Single 12 circle b) Single 24° circle c) Single 36° circle d) 12 24 and 36 circles with equal exposures

blurring out of unwanted detail (a 'thinner cut') while retaining clear depiction of structures within the tomographic layer This accords with the idea expressed by ÅSTRAND & REICHMANN that a low quantity of blurring may be compensated for, to some extent, by improving the blurring quality

On the whole the results confirm the expectation that the quality of blurring associated with the three-circle movement is superior to that produced by a simple circular movement

Computation of the transfer function in spiral tomography

Having shown that this approach allows prediction and control of blurring aberrations in linear and circular tomography, it would seem worthwhile to apply it to spiral tomography also The PSF in this case is a spiral line delta function whose form exactly matches the path of the source/film movement, and whose scale is simply related to the distance of the object section from the tomographic plane Attempts to find the transfer function by solving the Fourier transform integral analytically were unsuccessful However, the integral can be brought into a convenient form for subsequent numerical computation by the method described in the Appendix A Fortran computer programme was written to evaluate the transfer funcfions of spirals of arbitrary shape, so that the one whose Fourier transform shows the greatest freedom from sharp cut-off frequency points and phase distortions, could be determined by repeated trials

In the interests of time, consideration was limited at the outset only to regular spirals, having value when the polar co-ordinates (r, θ) are related by the equation

$$r = A\left(\frac{\theta}{2\pi}\right) + 1$$

(θ is a measured in radians) where A is a constant which specifies the shape of each spiral By taking advantage of the scaling property of Fourier transforms, this form of equation allows determination of the transforms of all possible regular spirals In the present investigation, the effects on the transfer function of varying A and also the total number N of whirls in the spiral were determined The transfer functions of various spirals, derived from Fourier transformation of the PSF are illustrated and discussed in the next section

Transfer functions of spirals As noted in the Appendix, it is advantageous to calculate the Fourier transforms of spirals as functions of the polar co-ordinates (ϱ, ϕ) in the spatial frequency plane Each transfer function presented below is therefore a cross-section through the origin of a 2D transform plotted against the radial spatial frequency co-ordinate ϱ, for a given value of ϕ

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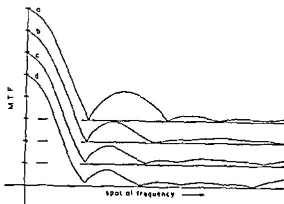


Fig 6

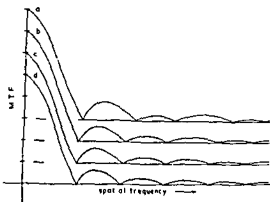


Fig 7

Fig 6 $\phi = 0$ section through the theoretical MTF of four regular spirals of different shape, assuming a PSF of constant height round the spiral The mean radius of each spiral is equal to unity, but the spirals become more open from (a) to (d) having values of the parameter A a) 0 5, b) 1 0, c) 1 5 and d) 2 0 Each spiral has three complete turns

Fig 7 See legend to Fig 6 The spirals assumed in this figure are each of 10 turns

the phase content of the transfer function is generally extremely important, it was considered that it could be neglected if the modulus of the transfer function was small ($<$ 10 per cent) In the low frequency maximum of the transfer function, where the phase part is significant owing to the high values of the modulus, the largest phase angle present was less than 25° in the worst case considered below Consequently the effect of phase distortions in this part of the transfer function should not be too serious in practice

Spirals with constant height PSF Fig 6 a–d show $\phi = 0$ cross-sections through the transfer functions of four 3 turn spirals, having values of A = 0 5, 1 0, 1 5 and 2 0

These transfer functions were calculated assuming the height of the PSF to be constant along the spiral, corresponding to constant radiation output per unit path length, and constant orbital speed of the source movement (Present day tomographic equipment is designed to give generally this type of behaviour) It is interesting to see how as A increases the height of the first secondary maximum decreases, from about 0 26 at A = 0 5 to about 0 15 at A = 2 This behaviour is to be expected, since as A approaches zero, the spiral degenerates into a circle having the transfer function illustrated in Fig 1, for which the secondary maximum height is 0 4

The question arises as to what improvement may be expected on increasing the number of turns in the spiral The transfer functions of four 10 turn spirals, having A = 0 5, 1 0, 1 5 and 2 0 appear in Fig 7

A similar type of behaviour to that noted in the previous case (N = 3) can be seen, except that the secondary maxima are more evenly spaced, and their heights decrease regularly with increasing spatial frequency It is interesting to note that Fig 7 d is indistinguishable from the function $J_1(x)/x$, which is the analytic transfer function of a disc-like PSF In other words, at least over this frequency range, there is no dif-

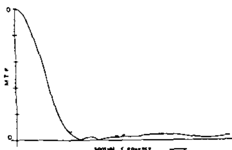


Fig 8 Two sections through the transfer function of a three turn spiral whose PSF falls in height in inverse proportion to the radial distance of the source from the centre of the spiral The continuous (a) and dashed (b) lines are the $\phi = 0$ and $\phi = 90$ sections respectively

ference in the blurring provided by a 10-turn spiral motion with A = 2 and an areal tomographic motion in which the source covers uniformly every point on the surface of a disc In fact, the transfer function for the three turn spiral with A = 2 (Fig 6 d) is itself quite similar to that of a disc Since a disc represents the limit of a spiral with an infinite number of turns these results show that there is no practical point in using spirals with values of A greater than 2 or N greater than 10

Spirals with varying height PSF In spite of including ten turns in the spiral, the transfer function illustrated in Fig 7 d still shows undesirable phase defects For further improvement in the form of the transfer function it is necessary to modify the PSF so that its height varies along the spiral Such a PSF may be obtained in practice either by varying the radiation output over the path of the spiral or by changing the orbital speed of the source Three different functional dependences of PSF on source position were investigated The first, considered above, was to keep the height of the PSF constant per unit path length (case 1) This implies that the exposure delivered in the outer turns of the spiral is greater than in the inner turns Since it has already been seen that even when there are a large number of turns in the spiral the transfer function (Fig 7 d) is still unsatisfactory, this dependence of PSF on source position was not considered further The second dependence (case 2) was that in which the height of the PSF varies in inverse proportion to the distance of the source from the centre of the spiral This corresponds to the case of a tube operated at constant current and moving round the spiral at constant angular velocity The exposure delivered in each turn of the spiral is approximately constant in this case The third dependence investigated (case 3) was that in which the PSF decreases linearly with the distance of the source from the centre of the spiral, in this case the exposure delivered for each complete turn of the spiral is less in the outer turns than in the inner turns, passing through a maximum in the turn midway between the centre of the spiral and its outer edge

From a technical point of view it is obviously advantageous to optimise both the quantity and quality of blurring for the smallest possible angular range of the tomographic movements This is achieved by keeping as much exposure as possible in the outer parts of the spiral, since these are predominantly responsible for the blurring

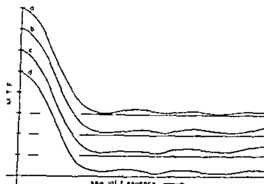


Fig 9 Sections at 45° intervals through the transfer function of a four-turn spiral whose PSF falls in height in inverse proportion to the radial distance of the source from the centre of the spiral a) 0, 180, b) 45°, 225°, c) 90°, 270°, d) 135°, 315°

quantity These considerations favour case 2 rather than case 3 Moreover, the degree of cancellation of the secondary maxima was found to be much better in the second case than in the third It was therfore decided to limit further consideration to case 2, corresponding to inverse proportionality between PSF and radial position of the source

The transfer function of the three-turn spiral $A = 2$ with radiation output varying as in case 2, is reproduced in Fig 8 a Comparison with Fig 6 d reveals a striking improvement in form of the transfer function, and it would seem at first sight to be sufficiently good to indicate the adoption of this type of spiral in future equipment Unfortunately, the spectrum was found to be seriously asymmetric, as is evident from Fig 8 b, which shows the $\phi = \pi/2$ section through the same transfer function Reducing the value of A to 1 0 was found to lessen the asymmetry of the spectrum, but the secondary maxima increased to an unacceptably large proportion (15 per cent) of the zeroth order peak height The spectrum of the ten-turn spiral $A = 2$, was found, as expected, to be highly symmetric, but it would obviously be advantageous to have as low a value of N as possible both to reduce the time taken for a complete exposure and to reduce the requirements imposed on the mechanical precision of the movement

The $N = 4$ spiral with $A = 2$ was considered to be a reasonable compromise between all the conflicting considerations noted above, and its spectrum, calculated at 45° intervals in the spatial frequency plane is reproduced in Fig 9 The height above background of the secondary maximum in the worst case ($\phi = \pi/2$) is 5 per cent of the zeroth order term, and it can be seen by inspection that this improves for other sections through the spectrum

Conclusions

The results of the previous section have indicated that the $N = 4$ spiral whose polar co-ordinates are related by the equation

$$r = 2\left(\frac{\theta}{2\pi}\right) + 1$$

(θ is measured in radians) and whose PSF decreases in inverse proportion to the value of the radial co-ordinate r of the source, should provide reliable blurring without too great complexity of movement It is impossible to say from this type of investigation whether or not this movement gives in some agreed sense optimum blurring, although it is clearly reasonably good and in principle superior to that available in present day equipment It is conceivable, though perhaps unlikely, that a different form of spiral or different dependence of PSF on source position would give an equivalent transfer function, in terms of blurring quality, with fewer turns of the spiral or a smaller value of A, both of which would make for a more practical system The present work is therefore merely another step towards optimising the character of tomographic blurring

Direct comparison of this work with that of ÅSTRAND & REICHMANN is difficult for several reasons Although they both rely at heart on the same principle, that of arranging the cancellation of blurring aberrations produced in one part of the spiral with those of another part, they each derive their results in fundamentally different ways The present investigation is mainly theoretically based whereas the work of ÅSTRAND & REICHMANN was largely empirical Although this means that they were unable to treat the spiral case exactly, as has been done here, their work has the advantage that the quality of blurring could be directly estimated by visual assessment of the film In the present case, the question of blurring fidelity has to be approached in a less direct way, since, although the blurring characteristics can be altered at will by varying the shape of the transfer function there is, as yet, no complete specification of the form of a non-perfect transfer function (perfect implying uniform amplitude and phase at all spatial frequencies) which nevertheless gives satisfactory images

Although it is true in principle that a transfer function could be modified at all frequencies to give blurring of any desired quality, this is an unrealistic goal to aim at since the necessary tomographic movement would probably be exceedingly complex Here it was chosen to correct the transfer function predominantly at low frequencies since the spectral content of radiographic images is generally largest in this region and other forms of blurring will in any case cause the response of the system to diminish towards high frequencies However, it may be that high frequency aberrations make more visual impact than low frequencies, or that 'beat' terms formed by interference of high frequency components could occasionally play a significant part

Nevertheless it is felt that such considerations, if found to be important, could readily be taken into account in future work, and that the transfer function approach represents a useful and objective way of choosing the form of the movement in spiral tomography

Appendix

It was stated in the text that the transfer function and point spread function are simply Fourier transforms of one another The purpose of this section is to derive an expression for the Fourier transform of a PSF which is a line delta function along the spiral path $r = 1 + A(\theta/2\pi)$

The transfer function, in terms of the variables k_x and k_y in the spatial frequency plane, is defined through the Fourier transform integral

$$T(k_x, k_y) = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} P(x, y) \exp\{-i[k_x x + k_y y]\} \, dx \, dy$$

This relationship may be expressed in a more convenient form for our purpose by transforming to the polar co-ordinates r, θ ϱ, ϕ in the spatial and frequency space domains Eq (1) then becomes

$$T(\varrho, \phi) = \int_0^{\infty}\int_0^{2\pi} P(r, \theta) r \exp\{-i\varrho r \cos(\theta - \phi)\} \, dr \, d\theta$$

Consider first the case when $P(r, \theta)$ is a circular line delta function of radius R and strength S per unit length

$$P(r) = \frac{S}{2\pi R a} \quad R < r < R + a \quad a \ll R$$

After performing the integration over r, it is found that

$$T(\varrho, \phi) = \frac{S}{2\pi}\int_0^{2\pi} \exp\{-i\varrho R \cos(\theta - \phi)\} \, d\theta$$

By virtue of the Bessel function identity

$$\int_0^{2\pi} \exp\{-i\xi \cos(\theta - \phi)\} \, d\theta = 2\pi J_0(\xi)$$

it is evident that $T(\varrho R) = S J_0(\varrho R)$

It can be seen that the ϕ co-ordinate of the transform has become redundant, i e the transform, like the original PSF is circularly symmetric

The spiral PSF can be tackled in a similar way In this case

$$P(r, \theta) = \frac{S(\theta)}{a} \quad 0 < \left[r - A\left(\frac{\theta}{2\pi}\right) - 1\right] < a \quad a \ll 1$$
$$= 0 \quad \text{Otherwise}$$

where the strength of the delta function has been written as θ dependent to allow for possible changes in the height of the PSF at different parts of the spiral

Since the only values of radius co ordinate r which survive the integration over r

are those which are related to θ by the equation $r = A(\theta/2\pi) + 1$ it is obtained on substituting,

$$T(\varrho, \phi) = \int_0^{2\pi} S(\theta)\left[A\left(\frac{\theta}{2\pi}\right) + 1\right] \exp\left\{-i\varrho\left[A\left(\frac{\theta}{2\pi}\right) + 1\right] \cos(\theta - \phi)\right\} d\theta$$

The real and imaginary parts of this expression may be numerically evaluated and its amplitude and phase may then be calculated in the normal way

It is stated in the text that symmetrical PSF's have wholly real transforms, i e the phase of the transform may take only the values of 0 and π radians It therefore follows that if the PSF is wholly real, as it must necessarily be if the radiation is incoherent, then the transfer function must be symmetric about the origin $(\varrho, \phi) = 0$

This implies that

$$T(\varrho, \phi) = T(\varrho, \phi \pm \pi)$$

This result is used in the legend to Fig 9

Acknowledgement

We would like to thank Dr W Simpson of the Department of Radiology, Newcastle General Hospital, for his helpful advice and comments, and Miss R Hunter and her staff for their able technical assistance This investigation was supported by a research grant from the Department of Health and Social Security

SUMMARY

In view of the close relationship [illegible] the transfer function, the transfer [illegible] movements have been calculated [illegible] spiral movement which yields blurring of favourable quality The validity of this approach has been demonstrated experimentally, by comparing the blurring characteristics of tomographs with single and multiple circular movements When the radii of the circles in the latter case are chosen with reference to the form of the transfer function, a marked improvement in blurring quality is apparent

ZUSAMMENFASSUNG

Es wurde im Hinblick auf die enge Beziehung zwischen den Bildabweichungen und der Form der Transferfunktion die Transferfunktionen einiger verschiedener Typen der spiralen formigen tomographischen Bewegungen numerisch berechnet Die Ergebnisse ermoglichen die Voraussage einer Form der spiralenformigen Bewegung, die zu einer Verschleierung vorteilhafter Qualitat fuhrt Die Richtigkeit dieser Annahme wurde experimentell durch den Vergleich der Charakteristika der Unschärfe von Tommogrammen bei einzelnen und multiplen kreisformigen Bewegungen nachgewiesen Wenn im letzteren Fall die Radien der Zirkel im Hinblick auf die Form der Transferfunktion gewahlt wurden, war eine wesentlich verbesserte Qualitat deutlich

RÉSUMÉ

En raison de l'étroite relation qui existe entre les aberrations de l'image et la forme de la fonction de transfert, les auteurs ont calculé numériquement les fonctions de transfert de différents types de mouvement tomographique spiralé Les résultats permettent de déterminer un type de mouvement spiralé qui donne un effacement de bonne qualité La validité de cette approche a été prouvée expérimentalement en comparant les caractéristiques d'effacement de tomographies faites avec des mouvements circulaires unique et multiples Dans ce dernier cas, quand les rayons des cercles sont choisis en tenant compte de la forme de la fonction de transfert, on constate une amélioration marquée de la qualité de l'effacement

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MODIFICATION OF THE BIOLOGIC DOSE TO NORMAL TISSUE BY DAILY FRACTION

Model for calculating normal tissue tolerance

M WOLLIN and A R KAGAN

The NSD was derived from the tolerance of normal skin (ELLIS 1969) Minor modifications of the coefficients of fraction number and time have been suggested for other normal tissues by (COHEN 1966, KAGAN et coll 1971 a, 1973) For the past six years it appeared that for the same 1 800 ret calculated by NSD, patients treated to similar volumes at 10 Gy/week (1 000 rad/week) or 7 5 Gy/week experienced different morbidity (KAGAN 1971) Many publications have suggested that the number of fractions and the daily dose is more important than overall time in determining differences in biologic effect (ELLIS 1968, ELKIND & WHITMORE 1967, UMEGAKI et coll 1974)

It was felt that a modification of the biologic model, NSD, for daily dose and time is necessary A modification which is now proposed is called BIR (Biologic Index of Reaction) BIR and NSD will be calculated for various normal tissue reactions and statistical correlation techniques will be used to compare the two models

From the Department of Radiation Therapy Southern California Permanente Medical Group Los Angeles, California 90027 U S A Submitted for publication 12 January 1976

RESUME

En raison de l étroite relation qui existe entre les aberrations de l image et la forme de la fonction de transfert les auteurs ont calculé numeriquement les fonctions de transfert de différents types de mouvement tomographique spiralé Les résultats permettent de de terminer un type de mouvement spirale qui donne un effacement de bonne qualite La validite de cette approche a ete prouvée experimentalement en comparant les caracteristi ques d effacement de tomographies faites avec des mouvements circulaires unique et mul tiples Dans ce dernier cas quand les rayons des cercles sont choisis en tenant compte de la forme de la fonction de transfert on constate une amélioration marquée de la qualite de l effacement

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Table 1

Patients with radiation myelopathy

NSD model			BIR model		
Range (ret_E)	No of patients	Per cent	Range (ret_{wk})	No of patients	Per cent
1 500–1 700	1/3	33	1 700–2 000	2/9	22
1 700–1 900	2/7	28	2 000–2 300	2/6	33
1 900–2 100	5/13	38	2 300–2 600	3/8	38
2 100–2 300	3/5	60	2 600–2 900	4/5	80

NSD
RPB +0 297
p is not significant at 0 05
RPB^2 – 8 8 %

BIR
RPB = +0 402
p>0 025
RPB^2 = 16 1 %

Data from DEN HOED-SUTSEMA et coll (1971)

The exponents A, B may be found from the Figure as

$$A = \frac{\ln \frac{\text{time}}{13\ 05\ \text{days}}}{10\ 181} \qquad (3)$$

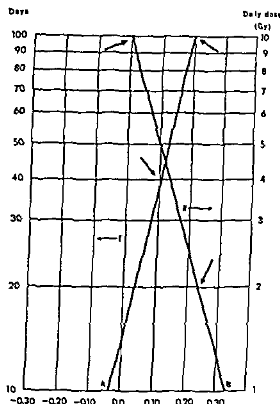
$$B = \frac{-\ln \frac{\text{daily dose}}{10\ \text{Gy}}}{6\ 706} \qquad (4)$$

where time is in days and daily dose in gray Using eq 2 and either the Figure or eqs 3, 4, BIR may be calculated BIR and NSD were found for radiation treatment schedules published in the literature

The correlation used—point biserial correlation (RPB)—is a standard statistical test which does not depend on how the data are grouped but is calculated point by point (BRUNING & KLINTZ 1968) A better correlation is defined when the RPB for BIR is positive and higher than that for NSD The significance of RPB (p) is tested by the Student s t-test In addition, the coefficient of determination (RPB^2), derived from RBP, tells us the per cent of the change in morbidity which is explained by the change in the biologic model (BAHN 1972) Although RPB is independent of data grouping, for discussion purposes only, the data will be grouped to calculate morbidity in per cent

in,
va

... the presence of a correlation significant at the 0 05 level



Graph for obtaining exponents A, B in BIR model The line for A was constructed so
at
str
0 24 and at 10 Gy/day 0 0 N = number of fractions T = total time in days

Method

The NSD requires knowledge of the total dose in Gy (D), number of fractions (N), total time in days (T) to calculate

$$NSD = \frac{D \times 100}{T^{.11} N^{.24}} (ret_E) \quad (1)$$

The present biologic model requires that the daily dose be known Then the Biologic Index of Reaction (BIR) is calculated

$$BIR = \frac{D \times 100}{T^A N^B} (ret_{wk}) \quad (2)$$

The line for B was constructed so that the exponent at 2 Gy/day is 0 24 and at 10 Gy/day is 0 0 The line for A was constructed so that the exponent at 40 days was 0 11 and at 100 days 0 20 These points (Figure, arrows) represent the present experience with tolerance doses and is in agreement with the animal, clinical and theoretical data of others (FOWLER 1971, LIVERSAGE 1971, FRIEDMAN 1974 a) *If the daily dose was greater than 2 Gy or the time much shorter or longer than 40 days significant differences in the value calculated by the two models occur* Increased irradiation injury seems to be better defined by BIR than by NSD

Table 3

Edema following irradiation of the vocal cord

NSD model			BIR model		
Range (ret_E)	No of patients	Per cent	Range (ret_{wk})	No of patients	Per cent
1 564	7/7	100	1 121	0 5	0
1 585	0/5	0	1 223	11/27	41
1 586	1/3	33	1 293	1/3	33
1 657	11/27	41	1 448	7/7	100

NSD
RPB = −0 202
p is not significant at 0 05
RPB^2 = 4 1 %

BIR
RPB = +0 536
p > 0 0005
RPB^2 = 28 7 %

Data from LOEFFLER (1974)

Table 4

Early edema following irradiation of carcinoma of the larynx

NSD model			BIR model		
Range (ret_E)	No of patients	Per cent	Range (ret_{wk})	No of patients	Per cent
1 700–1 800	6/17	35	1 200–1 600	0/3	0
1 800–1 900	3/16	19	1 600–2 000	9/30	30
1 900–2 000	6/16	38	2 000–2 400	6/16	37
2 000–2 100	6/8	75	2 400–2 800	6/8	75
2 100–2 200	6/6	100	2 800–3 200	6/6	100

NSD
RPB = +0 43
p 0 0005
RPB^2 = 18 5 %

BIR
RPB = +0 453
p < 0 0005
RPB^2 20 5 %

Data from KOK (1971)

parent The doses ranged from 60 to 71 4 Gy, total time from 42 to 59 days, fractions from 30 to 43 and daily dose from 1 6 to 2 Gy It is seen that NSD has little value in predicting edema, as the NSD numbers appear random The RPB is −0 202 This means as the NSD increases the possibility of edema decreases, clearly an unacceptable result BIR shows an RPB^2 of 29 per cent and the correlation is significant at the 0 0005 level BIR then shows a correlation where NSD does not

Table 4 summarizes the data of KOK (1971) of 63 patients treated for carcinoma

Table 2

Patients dead of radiation myelopathy

NSD model			BIR model		
Range (ret_E)	No of patients	Per cent	Range (ret_{wk})	No of patients	Per cent
1 200–1 400	1/4	25	1 500–2 000	0/3	0
1 400–1 600	1/3	33	2 000–2 500	2/6	33
1 600–1 800	4/6	66	2 500–3 000	4/4	100

NSD
RPB = +0 468
p is not significant at 0 05
RPB^2 = 21 9 %

BIR
RPB = +0 763
p > 0 005
RPB^2 = 58 3 %

Data from ATKINS & TRETTER (1966)

Results

Table 1 summarizes the data of DEN HOED-SUTSEMA et coll (1971) of 28 patients treated for pulmonary carcinoma Eleven patients developed myelopathy during a follow-up of two years The total dose to the spinal cord was from 55 to 76 Gy The fraction number range was from 20 to 33, the total time from 26 to 46 days and daily dose from 2 1 to 3 3 Gy In Table 1, it appears that there is little value of NSD for predicting the development of radiation myelopathy The percentage of patients with myelopathy appears random The RPB^2 is 9 per cent and the correlation is not significant at 0 05 level The BIR, however, does show value in predicting myelopathy There appears to be a steady risk of myelopathy with higher values of BIR Here the RPB^2 is 16 per cent and the correlation is significant at the 0 025 level

Table 2 summarizes the data of ATKINS & TRETTER (1966) of 7 patients treated for carcinoma of the breast, 2 patients for epidermoid carcinoma of the lung and one patient each for cylindroma of the trachea, carcinoma of the esophagus, adenocarcinoma of the lung and carcinoma of the base of the tongue who all developed myelopathy Six of the 13 died of myelopathy The total dose to the spinal cord ranged from 19 to 52 Gy, total time from 7 to 35 days, fraction from 2 to 26, daily dose from 2 to 11 9 Gy The NSD has little ability to predict which patients will die of myelopathy The RPB^2 is 22 per cent However, because of the small material, of only 13 patients, the correlation is not significant at the 0 05 level BIR has an RPB^2 of 58 per cent and the correlation is significant at the 0 005 level Thus BIR correlates better than NSD with death due to radiation myelopathy

Table 3 summarizes the data of LOEFFLER (1974) of 42 patients treated for vocal cord carcinoma, 19 of whom developed edema during treatment Four different dose time schedules were employed and therefore four groups of patients are ap-

Table 3

Edema following irradiation of the vocal cord

NSD model			BIR model		
Range (ret_E)	No of patients	Per cent	Range (ret_{wk})	No of patients	Per cent
1 564	7/7	100	1 121	0/5	0
1 585	0/5	0	1 223	11/27	41
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2 000–2 100	6/8	75	2 400–2 800	6/8	75
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Table 7

Summary of data comparing the correlation of morbidity with NSD or BIR

Morbidity	NSD			BIR		
	RPB	RPB² (per cent)	p	RPB	RPB² (per cent)	p
1 Myelitis (DEN HOED-SIJTSEMA et coll)	+0 297	8 8	*	+0 402	16 1	>0 025
2 Myelitis (death) (ATKINS & TRETTER)	+0 468	21 9	*	+0 763	58 3	>0 005
3 Larynx edema (LOEFFLER)	0 202	4 1	*	-0 536	28 8	>0 0005
4 Larynx edema (KOK)	0 430	18 5	0 0005	-0 453	20 5	>0 0005
5 Pericardial effusion (KAGAN et coll)	+0 278	7 7	0 005	+0 178	3 2	>0 05
6 Rib fracture (KOK)	+0 545	29 7	>0 0005	+0 568	32 3	>0 0005

* Not significant at the 0 05 level

Table 5 summarizes the data of KAGAN et coll (1971 b) of 109 patients who received radiation for Hodgkin s disease, 24 of whom developed pericardial effusion The total dose to the anterior surface of the heart varied from 34 Gy to 72 Gy, total time from 13 to 72 days, total fraction from 10 to 45, and daily dose from 1 5 to 5 7 Gy In both NSD and BIR the predictive value is not clinically remarkable In addition there is only a mild separation between absence and presence of pericardial effusion The RPB² for NSD is 7 7 per cent and the correlation is significant at the 0 005 level while RPB² for BIR is 3 2 per cent and the correlation is significant at the 0 05 level Thus BIR and NSD show a significant but low correlation

Table 6 summarizes the data of KOK (1971) for 54 inoperable cases of carcinoma of the breast who received radiation therapy and developed rib fracture The total dose in the treated volume ranged from 49 to 65 Gy, total time from 30 to 49 days, total fractions from 14 to 22 and daily dose from 2 6 to 3 4 Gy All patients were treated three times per week Both NSD and BIR show comparable results The RPB² for NSD is 29 7 per cent and the correlation is significant at the 0 0005 level while BIR has a slightly higher RPB² of 32 3 per cent and the correlation is significant at the 0 0005 level

A summary of all the data is presented in Table 7

Discussion

The attempt to express all b[illegible] all treatment time and number [illegible] by STRANDQVIST (1944) and h[illegible] [illegible] by FRIEDMAN & PEARLMAN (1955),

Table 5

Pericardial effusion following irradiation of Hodgkin's disease

NSD model			BIR model		
Range (ret_E)	No of patients	Per cent	Range (ret_{wk})	No of patients	Per cent
1 100–1 400	0/3	0	0–1 000	0/1	0
1 400–1 600	2/23	9	1 000–2 000	7/39	18
1 600–1 800	8/43	19	2 000–3 000	12/59	20
1 800–2 000	9/25	36	3 000–4 000	4/8	50
2 000–2 400	5/15	33	4 000–5 000	1/2	50

NSD	BIR
RPB = +0 278	RPB = +0 178
$p > 0\ 005$	$p > 0\ 05$
$RPB^2 = 7\ 7$ %	$RPB^2 = 3\ 2$ %

Data from KAGAN et coll (1971)

Table 6

Rib fracture following irradiation of carcinoma of the breast

NSD model			BIR model		
Range (ret_E)	No of patients	Per cent	Range (ret_{wk})	No of patients	Per cent
1 600–1 800	0/14	0	1 800–2 100	0/30	0
1 800–2 000	2/30	7	2 100–2 400	2/12	16
2 000–2 200	6/10	60	2 400–2 700	6/12	50

NSD	BIR
RPB = +0 545	RPB 0 568
$p > 0\ 0005$	p 0 0005
$RPB^2 = 29\ 7$ %	RPB^2 32 3 %

Data from KOK (1971)

of the larynx who developed early edema The total dose for all patients was 63 Gy The patients were treated either 3 or 5 fractions per week for a total fraction range of 16 to 36 fractions The total time was from 35 to 58 days and the daily dose ranged from 1 75 to 3 85 Gy It is seen that the NSD is of some value in predicting morbidity The RPB^2 is 18 5 per cent and the correlation is significant at the 0 0005 level BIR shows a similar correlation, the RPB^2 is 20 5 per cent and the correlation is significant at the 0 0005 level

Table 7

Summary of data comparing the correlation of morbidity with NSD or BIR

Morbidity	NSD			BIR		
	RPB	RPB^2 (per cent)	p	RPB	RPB^2 (per cent)	p
1 Myelitis (DEN HOED SUTSEMA et coll)	+0 297	8 8	*	+0 402	16 1	>0 025
2 Myelitis (death) (ATKINS & TRETTER)	+0 468	21 9	*	+0 763	58 3	>0 005
3 Larynx edema (LOEFFLER)	−0 202	4 1	*	+0 536	28 8	>0 0005
4 Larynx edema (KOK)	+0 430	18 5	>0 0005	+0 453	20 5	>0 0005
5 Pericardial effusion (KAGAN et coll)	+0 278	7 7	>0 005	+0 178	3 2	>0 05
6 Rib fracture (KOK)	+0 545	29 7	>0 0005	+0 568	32 3	>0 0005

* Not significant at the 0 05 level

Table 5 summarizes the data of KAGAN et coll (1971 b) of 109 patients who received radiation for Hodgkin s disease, 24 of whom developed pericardial effusion The total dose to the anterior surface of the heart varied from 34 Gy to 72 Gy, total time from 13 to 72 days, total fraction from 10 to 45, and daily dose from 1 5 to 5 7 Gy In both NSD and BIR the predictive value is not clinically remarkable In addition there is only a mild separation between absence and presence of pericardial effusion The RPB^2 for NSD is 7 7 per cent and the correlation is significant at the 0 005 level while RPB' for BIR is 3 2 per cent and the correlation is significant at the 0 05 level Thus BIR and NSD show a significant but low correlation

Table 6 summarizes the data of KOK (1971) for 54 inoperable cases of carcinoma of the breast who received radiation therapy and developed rib fracture The total dose in the treated volume ranged from 49 to 65 Gy, total time from 30 to 49 days, total fractions from 14 to 22 and daily dose from 2 6 to 3 4 Gy All patients were treated three times per week Both NSD and BIR show comparable results The RPB for NSD is 29 7 per cent and the correlation is significant at the 0 0005 level while BIR has a slightly higher RPB^2 of 32 3 per cent and the correlation is significant at the 0 0005 level

A summary of all the data is presented in Table 7

Discussion

The attempt to express all [illegible] all treatment time and number [illegible] by STRANDQVIST (1944) and has been modified by FRIEDMAN & PEARLMAN (1955),

COHEN (1952), ELLIS (1967) The NSD model has been accepted and employed in many radiation therapy centers as a guide in treating patients and evaluating results

Many questions, however, still have to be answered (SHULZ et coll 1975) Two questions of special interest will be discussed here

1) The first one is whether the recovery coefficient for the fraction number changes with the daily dose KAGAN et coll (1976) in irradiation of the dog brain found that even though the NSD was equal, changing the daily dose by a factor of two yielded different biologic results UMEGAKI et coll felt that in evaluating radiation tolerance of the human larynx a correction had to be made for the size of the daily dose By decreasing the recovery coefficient for N for large daily doses BIR is increased markedly

2) The second one is if the recovery coefficient for time changes with the overall time It is believed that repopulation of cells occurs during the time between the daily doses It was suggested by DUTREIX et coll (1971) that a steady state might be reached in humans where growth of cells would balance out destruction LAJTHA & OLIVER (1961) also postulated such a possibility FRIEDMAN (1974 b) felt that it was possible that during a radiation course with a low daily dose, the recovery process accelerates and neutralizes the daily destructive dose so that a healing phase commences after one month despite continuing radiation Consequently, as overall time increases, the biologic effect may decrease due to the compensating cell kinetics of the normal tissue This possible effect would change the recovery coefficient for time LIVERSAGE has suggested the use of variable values for the time exponent

WINSTON et coll (1969) state that NSD holds only for a treatment time within the range of 3 to 100 days FOWLER (1973), felt that 'the NSD formula applies well to normal tissue reactions, especially of skin and mucosa, at levels of injury approaching tolerance reactions, after irradiation between 3 and 30 equal intervals and in an overall time not exceeding about two months' By increasing the recovery coefficient of T, for long overall treatment times, BIR decreases markedly However, the daily dose changes BIR more than the overall time because fraction size seems to be more important Of course, other factors may influence the determination of biologic dose such as volume of irradiated tissue, oxygenation, cell cycle, repair potential, different recovery coefficients for different tissues While these factors were not taken into account perhaps another model could be devised that would be able to incorporate them successfully

The analysis of clinical data indicates that the size of the daily dose and overall treatment time is important for certain types of morbidity In radiation myelitis (Tables 1, 2) and morbidity in treating vocal cord carcinoma (Tables 3, 4), the increasing per cent of radiation injury is explained better with BIR than NSD The RPB^2 values in Table 7 support this

The BIR values for radiation myelopathy (Table 1) indicate that at 1 700 to 2 000 ret_{wk} myelopathy starts and over 2 600 ret_{wk} myelopathy is almost certain Of those that develop myelopathy (Table 2) at 2 000 to 2 500 ret_{wk} some will die and over

2 500 ret_{wk} it is almost certain all will die The BIR values for edema in treating vocal cord (Table 3) indicate a range of 1 100 to 1 450 ret_{wk} for no edema to 100 per cent edema while Table 4 indicates 1 200 to 3 200 ret_{wk} for the same morbidity The explanation for the differing ranges might lie in the different lesions, T1 only (KOK), T1–T4 (LOEFFLER), different machines, Cobalt (KOK), Betatron (LOEFFLER) and different field sizes, 5 cm × 6 cm (KOK), 12 cm × 6 cm for T4 lesions (LOEFFLER), LOEFFLER used bolus, but not KOK However, the radiation pericardial effusion data (Table 5) are explained inadequately by BIR or NSD Neither model appears to show a strong correlation with morbidity The morbidity in breast carcinoma (Table 6) is explained in a comparable manner by either NSD or BIR A volume factor is not absolutely essential for the BIR model to predict myelopathy or laryngeal edema It may be, however, that a volume factor in breast carcinoma morbidity or the amount of tumor cells present in pericardial effusion is essential to understand the results These possibilities have already been suggested (FOWLER 1973, PEREZ TOMAYO et coll 1974, KOK, KAGAN et coll 1971 b, EADS 1972)

There appears to be a limited amount of clinical material available to analyse time-dose relationships All factors of time, dose, fraction number and other clinical data (stage, histology, etc) that might influence normal tissue injury should be listed Results expressed only in NSD ret_E may hide other biologic effects that the NSD model may not adequately explain

When the model predicts morbidity, it can be used to equate different treatment regimes with the aid of such concepts as TDF (ORTON 1973) If the model does not predict morbidity, different treatment schedules cannot be said to be equal

All models of biologic effect should be tested against clinical information When the model adequately explains the clinical situation, then it could be used clinically Reasoning by laboratory animal experiments, and in vitro experiments, should not substitute for confirmation in clinical practice

Conclusions

Some modification to the model for normal tissue injury should be made for the daily dose and overall time BIR is an attempt to do this It appears that some normal tissue injury may be explained better with BIR than NSD (radiation myelopathy, vocal cord edema) Some tissue injury is not explained well by either BIR or NSD (pericardial effusion), but some tissue injury is explained adequately by either NSD or BIR [illegible]

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SUMMARY

A method to predict normal tissue injury is proposed that includes high daily doses and unusual times successfully by calculating a new value called BIR (Biologic Index of Reac-

tion) BIR and NSD were calculated for various normal tissue reactions With the aid of statistical correlation techniques it is found that the BIR model is better than the NSD model in predicting radiation myelopathy and vocal edema and as good as NSD in predicting rib fracture Neither model predicts pericardial effusion In no case were the results of BIR inferior to those of NSD

ZUSAMMENFASSUNG

Eine Methode die Schädigung des normalen Gewebes vorauszusagen wird vorgelegt die hohe tägliche Dosen und ungewohnliche Zeitfolgen erfolgreich einschliesst dabei wird ein neuer Wert BIR (Biologic Index of Reaction) genannt berechnet BIR und NSD wurden fur verschiedene Normalgewebereaktionen berechnet Mit *Hilfe einer statistischen Kor*relationstechnik wurde gefunden dass das BIR Modell besser als das NSD Modell bei der Voraussage einer Strahlenmyelopathie und eines Oedems des Stimmbandes und ebenso gut wie das NSD *Modell* bei der Voraussage einer Rippenfraktur ist Keines der Systeme lasst einen Pericarderguss voraussagen In keinem Fall verhielt sich das BIR System schlechter als das NSD System

RÉSUMÉ

Les auteurs proposent une méthode pour prévoir les lésions du tissu normal sous l effet *de hautes doses quotidiennes et de durée inhabituelle en calculant une nouvelle valeur ap*pelee BIR (Index Biologique de Réaction) Le BIR et la NSD ont été calculés pour différentes réactions du tissu normal Avec l aide des techniques de corrélation statistique les auteurs ont constaté que le modèle BIR est meilleur que le modèle *NSD* pour prévoir *la* myélopathie et l oedème des cordes vocales dû aux radiations et aussi bon que la NSD pour prévoir la fracture de cotes Aucun de ces modèles ne prévoit l épanchement péricardique Dans aucun cas le BIR n a été inférieur à la NSD

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FORMING OF ELECTRON BEAMS FROM A BETATRON BY FOIL SCATTERERS

A P KOZLOV and V A SHISHOV

Experimental evidence has shown foil scatterers to be a most convenient means for forming the electron beam generated by a betatron Though the problems of the forming of fast electron beams have been previously discussed (LINDSKOUG et coll 1971, OKUMURA et coll 1967, SVENSSON 1971), the potentialities of this method have not yet been exhausted

This report deals with a technique for electron beam forming by means of two foil scatterers

Experimental

The experiments were performed on the type B5M-25 betatron A more detailed description of the forming technique is presented in the report of KOZLOV & SHISHOV (1972)

Fig 1 illustrates schematically the formation of an electron beam generated by the B5M 25 betatron On leaving the vacuum chamber, the electron beam is expanded by foil scatterers located at the collimator entry The complete set comprises three foils encased in special holders Two holders are slidably mounted in guide slots and may be displaced by means of a single device The third one is rigidly fixed in front of the aperture of the entrance diaphragm Four combinations of the positions of two movable foils and one fixed giving adequate expansion at four energies, are allowed

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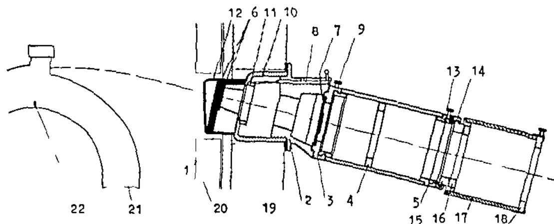


Fig 1 The electron beam from a B5M 25 betatron 1—entrance diaphragm of collimator 2—intermediate diaphragm body, 3, 4 5—diaphragms, 6—scattering foils, 7—compensator, 8—foil scatterer fixing device, 9—screw, 10—diaphragm mount, 11—ionization chamber of monitor, 12—protective casing, 13—fixing screw, 14—connector, 15—tube flange (*aluminium, 30 mm thickness*) 16—additional absorber (brass, 8 mm thickness) 17—tube wall (perspex, 10 mm thickness) 18—exit diaphragm of tube, 19—lead absorber, 20—bremsstrahlung collimator, 21—vacuum chamber 22—bremsstrahlung producing target

The scatterer thicknesses are selected so as to ensure an adequate expansion by the fixed foil at 10 MeV, whereas a combination of the fixed foil with either of the moveable ones should give the same expansion at 15 and 20 MeV The ratio of the total foil thicknesses necessary at two different energies is approximately equal to the ratio of the two energies squared when the same mean square angle of scattering is desired (cf eq 5), thus

$$t_1\ t_2 = E_1^2\ E_2^2,$$

i e the following conditions are met with $t_2 - 2\ 25\ t_1$, $t_3 = 4\ t_1$

In the case of the fourth energy

$$t_4 = t_1 + 1\ 25\ t_1 + 3\ t_1 - 5\ 25\ t_1$$

is obtained

The foil of such a thickness gives an adequate expansion at 23 MeV

Apart from the said scattering foils, the beam is further equalized by specially designed scatterers or compensators The compensator is an oval or rectangular piece of foil glued on a thin substrate made of some light material, e g aluminium, perspex, or cardboard The compensator is mounted at some distance from the fixed foil and its centre is aligned with the beam axis The treatment field is equalized by scattering electrons out of the central core of the beam with a compensator Since the foil substrate is designed not to affect the electron distribution substantially, the term 'compensator' refers to the central part only

The use of compensators produces a large-size uniform field with much less losses in output as compared with the conventional single-foil scatterer The electron



Fig 2. Distribution of ionization in air perpendicular to the beam axis at the treatment distance 1—oval compensator d_k 25 cm $\tau_x = 3\,9$ cm, $\tau_y = 5\,2$ cm, t_k 0 15 mm Cu, $R_{zt} = 8$ cm $t = 0\,4$ mm Cu 2—without compensator copper foil $t = 2$ mm Cu

beam distribution over the treatment field as measured by means of an ionization chamber appears in Fig 2 Curve 1 was obtained from a combined application of a 0 15 mm thick copper compensator and a 0 4 mm thick (t_3) copper foil Curve 2 was obtained by means of one 2 mm thick copper scattering foil Before being scattered by the foil electron energies were the same As seen from the figure a field of about 16 cm along x axis was irradiated with a maximum dose variation of 10 per cent in both cases However the loss in output involved in the application of the compensator was 3 5 times less than in the case of one 2 mm thick copper foil Moreover, application of compensators reduces the losses of energy as well as the background of concomitant bremsstrahlung considerably Fig 3 shows central axis *depth dose* distribution measured by means of an 0 1 cm³ ionization chamber in a water phantom under the conditions mentioned Curve 1 was obtained by using the compensator, whereas curve 2 by using the 2 mm thick copper foil A comparison of the above dose distributions shows that the bremsstrahlung background at the *end of electron* path for the 2 mm thick foil is 2 to 2 5 times higher and the practical range R_p is nearly 1 cm shorter The useful therapeutic region of the depth dose curves, i e the region containing doses in excess of 80 per cent is also markedly *smaller*

The use of compensators improves the form of the electron beam considerably Fig 4 a demonstrates the isodose curves found by means of an automatic isodose recorder in a water phantom transversely to the beam axis The area enclosed by the 80 per cent curve actually coincides with the geometric limits of the therapeutic field Isodose curves measured along the beam axis appear in Fig 4 b Since electrons of the beam core pass through a thicker layer *and lose more* energy than those round

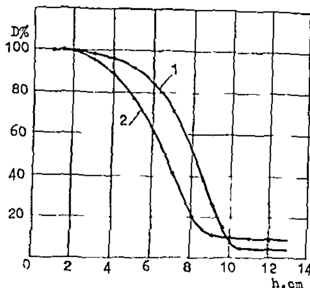


Fig 3 Relative depth dose curves measured in a water phantom 1—oval compensator, $\tau_x = 3.9$ cm, $\tau_y = 5.2$ cm, $t_k = 0.15$ mm Cu 2—copper foil, t = 2 mm Cu The electron energies before the scattering foils are the same

the beam periphery, the core isodoses are somewhat closer to the surface However, Fig 4 b reveals that the therapeutic field distortion is insignificant

Theoretical considerations

The mechanism of the compensator effect may be considered in more detail by introducing coordinate systems xyz, $x_k y_k z_k$ and x'y'z' so that the xy-plane is the plane of the scattering foil, $x_k y_k$—with that of the compensator, and x'y'—with that of the therapeutic field (Fig 5) Suppose that axes z, z_k and z' are directed along the beam axis Further, the following symbols will be used 2a × 2b—dimensions of collimator entrance diaphragm aperture, D—scatterer to surface distance, d_k—scatterer to compensator distance, τ_x and τ_y—compensator sizes along x_k and y_k axes, respectively, and L—extrapolated source to scattering foil distance (In this case, the distance to the extrapolated source is equal to that to the tube window of betatron vacuum chamber)

All electrons, passing through the plane of therapeutic field x'y' may be divided, as a first approximation, into (a) particles which have bypassed the compensator $j_1(x', y')$ and (b) particles, which have been subjected to scattering $j_2(x', y')$

The actual fluence at an arbitrary point of the therapeutic field $j_k(x', y')$ is obtained by summing functions $j_1(x', y')$ and $j_2(x', y')$

The angular distribution of the narrow mono-directional beam of electrons after transmission through the foil scatterer in projections on orthogonal axes α_1 and α_2, which lie in a plane perpendicular to the direction of incidence, is known to be of the following form (Bethe & Ashkin 1953)

$$P_1(\alpha_1)\,d\alpha_1 = \frac{1}{\sqrt{2\pi\overline{\alpha_1^2}}}\exp\left(-\frac{\alpha_1^2}{2\overline{\alpha_1^2}}\right)d\alpha_1 \qquad (1)$$

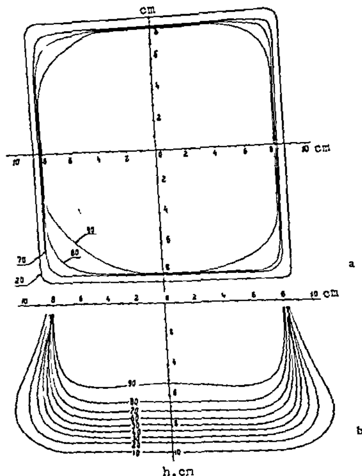


Fig 4 Isodose curves in a compensator formed beam a) Transversally to the beam axis in a water phantom at 2 cm depth, b) Longitudinally, field 16 cm × 16 cm, compensator is similar to the one in Fig 3

The statistical distribution of α_2 projections is similar to that of α_1 projections. Therefore, $2\overline{\alpha_1^2} = 2\overline{\alpha_2^2} = \bar\theta$ The magnitude $\bar\theta$ is described by the formula

$$\overline{\theta^2} = 0.157\frac{Z(Z+1)}{A}\frac{t}{E^2}\ln(1.13 \times 10^4 Z^{4/3} A^{-1} t) \tag{2}$$

where Z and A designate the atomic number and weight of the foil material, E the electron energy (MeV) and t the foil thickness (g/cm²)

For an elementary beam of electrons emitted from the area dxdy with the centre at x, y, the values of α_1 and α_2 may be written in the following form

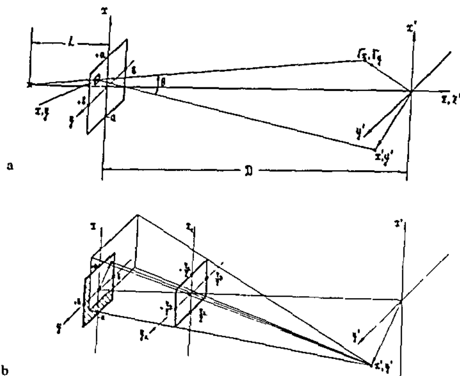


Fig 5. Geometry of forming of electron beam by scattering foil and compensator

$$\alpha_1 \approx \frac{x' - \gamma x}{D}; \quad \alpha_2 \approx \frac{y' - \gamma y}{D} \tag{3}$$

where

$$\gamma = \frac{D + L}{L} \tag{4}$$

The factor γ is introduced to correct for the initial divergence of the yet unformed electron beam Physically, the appearance γ implies the convergence of the axes of all elementary beams at the focus (Fig 5 a)

Taking into account eq 3, the statistical distribution of the beam emitted from the area dxdy along the coordinates x′ and y′ without compensator, is as follows

$$P_{xy}(x', y')\,dx'\,dy' = \frac{1}{\pi \overline{\theta^2} D^2} \exp\left(-\frac{(x' - \gamma x)^2 + (y' - \gamma y)^2}{D^2 \overline{\theta^2}}\right) dx'\,dy' \tag{5}$$

The electron fluence at x′, y′ is found by multiplying the obtained distribution value by j(x, y)dxdy (the fluence of electrons emitted from area dxdy) and integrating over the entire exposed area of the foil

$$j(x', y') = \frac{1}{\pi \overline{\tau'^2}} \iint_S j(x, y) \exp\left(-\frac{(x' - \gamma x)^2 + (y' - \gamma y)^2}{\overline{\tau'^2}}\right) dx\,dy \tag{6}$$

where

$$\overline{\tau'^2} = D^2 \overline{\theta^2}. \tag{7}$$

The fluence $j(x, y)$ of electrons emitted from B5M-25 betatron within the ranges of $-a$ to $+a$ and $-b$ to $+b$ may be approximated by

$$j(x, y) = j_0 e^{(x^2/\overline{x^2})} \tag{8}$$

where x is rectangular to the orbital plane of the betatron

Integration of eq 6 yields

$$j(x', y') = \frac{1}{4\gamma^2 \delta \sqrt{\overline{\tau^2}}} j_0 \exp\left(-\frac{x'^2}{\overline{\tau^2} + \gamma^2 \overline{x^2}}\right)$$

$$\times \left[\Phi\left\{\left(a\gamma\delta + \frac{x'}{\delta\overline{\tau^2}}\right)\sqrt{2}\right\} + \Phi\left\{\left(a\gamma\vartheta - \frac{x'}{\delta\overline{\tau'^2}}\right)\sqrt{2}\right\}\right]\left[\Phi\left\{\frac{b\gamma + y'}{\sqrt{\overline{\tau^2}}}\sqrt{2}\right\} + \Phi\left\{\frac{b\gamma - y'}{\sqrt{\overline{\tau^2}}}\sqrt{2}\right\}\right] \tag{9}$$

where $\Phi\{U\}$ is an integral of probability

$$\Phi\{U\} = \frac{2}{\sqrt{2\pi}} \int_0^U e^{-(V^2/2)} dV, \tag{10}$$

$$\delta = \sqrt{\frac{1}{\gamma^2 \overline{x^2}} + \frac{1}{\overline{\tau'^2}}} \tag{11}$$

The fluence of particles bypassing the compensator $J_1(x', y')$ is found in a similar manner If air scattering is neglected, the motion of the foil scattered electrons may be assumed to be rectilinear Therefore, in the case of those electrons which bypass the compensator, the vicinity of the point x', y' may be reached only by those particles, which pass through an area (cross-hatched area in Fig 5 b) 'visible' from x', y Hence, integration in eq 6 should be performed with respect to the 'visible' area of the 'source only If the complete scattering foil is 'seen' from x', y', the integral is chosen from $-a$ to $+a$ with respect to x and from $-b$ to $+b$ with respect to y and its value coincides with eq 9

When an observation is carried out from the penumbra region, where the source is partially overlapped by the compensator, integration should not include the area of the intersection of the source and the projection of the compensator on xy-plane from x'y (Fig 5 b) And, finally, if an observation is carried out from the area of shadow, $j_1(x', y) = 0$

To simplify the matters, the distribution along x'- and y'-axes alone will be considered, assuming that $x' \geq 0$ and $y' \geq 0$ At $x < 0$, $y' < 0$ of the distribution may be found from geometric considerations Find the fluence $J_1(x', y')$ for a rectangular compensator (Fig 6, type a) The coordinates of the projections of the compensator boundaries on xy-plane are determined from the following equations

$$X_k^{1,2} = \frac{d_k}{D - d_k} x' \pm \frac{D}{D - d_k} \frac{\tau_x}{2}, \quad Y_k^{1,2} = \frac{d_k}{D - d_k} y' \pm \frac{D}{D - d_k} \frac{\tau_y}{2} \tag{12}$$

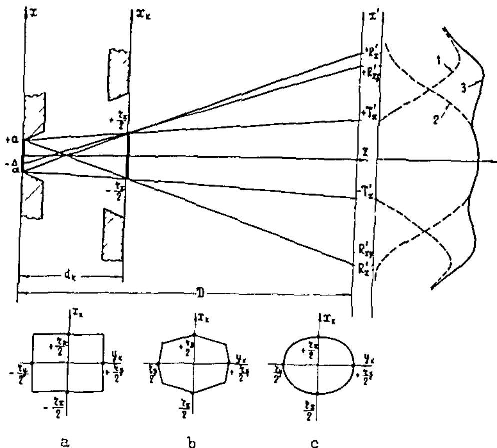


Fig 6 Geometry of the equalization with a compensator of the therapeutic field 1—fluence of electrons bypassing compensator $j_1(x', y)$, 2—fluence of electrons scattered by compensator $j_2(x', y')$, 3—total distribution $j_k(x', y')$ a, b, c) Different performances of the compensators

Substituting the values of $X_k^{1\,2} = \pm a$, $Y_k^{1\,2} = \pm b$ in eq 12, the boundaries of the area of shadow T′ and penumbra R′ along x′- and y′-axes are obtained

$$R'_x = \frac{D}{d_k}\left(\frac{\tau_x}{2} + a\right) - a, \quad T'_x = \frac{D}{d_k}\left(\frac{\tau_x}{2} - a\right) + a$$

$$R'_y = \frac{D}{d_k}\left(\frac{\tau_y}{2} + b\right) - b \quad T_y = \frac{D}{d_k}\left(\frac{\tau_y}{2} - b\right) + b \tag{13}$$

Thus, for $x' < T'_x$ the fluence $j_1(x', y'=0) = 0$, whereas for $x' \geq R'_x$ $j_1(x', y'=0) = j(x', y'=0)$, where $j(x', y'=0)$ is found from eq 9 Similar conditions hold true for y′ direction as well The fluence in the penumbra region ($T_x < x' < R'_x$, $y'=0$ or $x'=0$, $T'_y < y' < R'_y$) is easy to obtain from eq 9 by integration limit substitution Substituting X'_k for $-a$ and Y'_k for $-b$,

$$j_1(x', y'=0) = \frac{1}{2\gamma^2\delta\sqrt{\overline{\tau^2}}} j_0 \exp\left(-\frac{x'^2}{\overline{\tau^2} + \gamma^2\overline{x^2}}\right) \times \left[\Phi\left\{\left(\frac{x'}{\delta\overline{\tau^2}} - X_k^1\gamma\delta\right)\sqrt{2}\right\} + \Phi\left\{\left(a\gamma\delta - \frac{x'}{\delta\overline{\tau^2}}\right)\sqrt{2}\right\}\right] \Phi\left\{\frac{b\gamma\sqrt{2}}{\sqrt{\overline{\tau^2}}}\right\} \tag{14}$$

is obtained

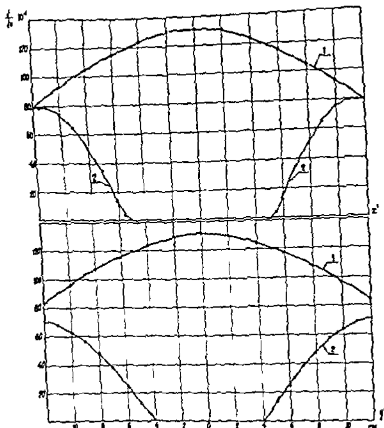


Fig 7 Fluence of electrons at the treatment distance 1—foil-scattered electrons, without compensator $j(x', y')$ 2—electrons bypassing the compensator $j_1(x', y')$

$$j_1(x'=0, y') = \frac{1}{2y^2\delta\sqrt{\overline{\tau^2}}} j_0 \Phi\{a\gamma\delta\sqrt{2}\} \times \left[\Phi\left\{\frac{y'-\gamma Y_k^1}{\sqrt{\overline{\tau^2}}}\sqrt{2}\right\} + \Phi\left\{\frac{b\gamma - y'}{\sqrt{\overline{\tau^2}}}\sqrt{2}\right\}\right] \quad (15)$$

Fig 7 illustrates the fluence $j(x', y')$ without compensator and that of electrons bypassing the compensator $j_1(x', y')$ Both functions were obtained by means of eqs 9 12, 14 and 15 for a 0 34 mm thick lead scattering foil and compensator ($\tau_x = 5\ 2$ cm, $\tau_y = 6\ 0$ cm at $2a \times 2b = 3$ cm $\times$ 5 cm, D = 80 cm, $d_k = 25$ cm, E = 20 MeV) The value of $\sqrt{\overline{x^2}}$ found by photometric measurements of the electron beam in the foil scatterer plane (L = 40 cm) was 2 0 cm

For the lead compensator, eq 7 takes the form

$$\overline{\tau^2} = 11\ 9 \frac{D^2}{E^2} t(4.29 - \lg t) \quad (16)$$

Substituting foil thickness in g/cm², values of D in cm and E in MeV, we get $\overline{\tau'^2} = 285$ cm²

The projections of the compensator boundaries are found from the equations

$$X_k^1 = 1\ 455\frac{\tau_x}{2} - 0\ 455\, x', \quad Y_k^1 = 1\ 455\frac{\tau_y}{2} - 0\ 455\, y'$$

The distribution of electrons subjected to additional scattering influence of the compensator may be determined by means of computation of the fluence $j(x_k, y_k)$ in the compensator plane It is described by an equation similar to 9, the value of d_k being substituted for D The values of γ, $\overline{\tau'^2}$ and δ are changed, accordingly

$$\gamma_k = \frac{d_k + L}{L}, \quad \overline{\tau_k^2} = \overline{\theta^2}\, d_k^2 = \overline{\tau^2}\frac{d_k^2}{D^2}, \quad \delta_k = \sqrt{\frac{1}{\gamma_k^2 \overline{x}} + \frac{1}{\overline{\tau_k}}} \tag{17}$$

For further convenience, eq 9 is approximated in the ranges of $-(\tau_y/2)$ to $+(\tau_y/2)$ and of $-(\tau_x/2)$ to $+(\tau_x/2)$ by a simpler function

$$j(x_k, y_k) \approx j^a(x_k, y_k) = N_k \exp\left(-\frac{x_k^2}{\overline{x_k^2}} - \frac{y_k^2}{\overline{y_k^2}}\right) \tag{18}$$

Taking into account eqs 17 and 18, the following may be obtained

$$N_k = j(x_k = 0, y_k = 0) = \frac{1}{\gamma_k^2 \delta_k \sqrt{\overline{\tau_k}}}\, j_0\, \Phi\{a\gamma_k \delta_k \sqrt{2}\}\, \Phi\left\{\frac{b\gamma_k \sqrt{2}}{\sqrt{\overline{\tau_k^2}}}\right\} \tag{19}$$

The values of $\overline{x_k^2}$ and $\overline{y_k^2}$ are determined by the fluence magnitude at compensator boundaries

$$N_k \exp\left(-\frac{\tau_x^2}{4\overline{x_k^2}}\right) = j\left(x_k = \frac{\tau_x}{2}, y_k = 0\right), \quad N_k \exp\left(-\frac{\tau_y^2}{4\overline{y_k^2}}\right) = j\left(x_k = 0, y_k = \frac{\tau_y}{2}\right) \tag{20}$$

Eqs 19 and 20 yield all the parameters included into the approximate function $j^a(x_k, y_k)$

Introduce symbols

$$\overline{k^2} = \overline{\theta_k^2}(D - d_k)^2 \tag{21}$$

where $\overline{\theta_k^2}$ = mean-square angle of scattering in the compensator

$$\lambda = \frac{D}{d_k} \tag{22}$$

The precise determination of the fluence $j_2(x', y')$ is complicated, because this function is expressed by the four-fold integral with respect to the area of the foil scatterer and compensator, which cannot be reduced to elementary functions There fore, it seems appropriate only to consider an approximate method of calculation

Assuming the scattering foil centre to be the focal point of the fluence incident on the compensator, j_2 may be written in analogy with eq 6

$$j^{a}(x', y') = \frac{1}{\pi \overline{k^2}} \int_{-(\tau_x/2)}^{+(\tau_x/2)} d\tau_k \int_{-(\tau_y/2)}^{+(\tau_y/2)} dy_k j^{a}(x_k, y_k) \exp\left(-\frac{(x' - \lambda x_k)^2 + (y' - y\lambda_k)^2}{\overline{k^2}}\right) \quad (23)$$

Hence, after integration

$$j^{a}(x', y') = \frac{N_k}{4\overline{k^2}\lambda^2 \omega\varrho} \exp\left\{-\frac{x'^2}{\overline{k^2} + \lambda^2 \overline{x_k^2}} - \frac{y'^2}{\overline{k^2} + \lambda^2 \overline{y_k^2}}\right\}$$

$$\times \left[\Phi\left\{\frac{\lambda\tau_x}{\sqrt{2}}\omega + \frac{x'\sqrt{2}}{\overline{k^2}\omega}\right\} + \Phi\left\{\frac{\lambda\tau_x}{\sqrt{2}}\omega - \frac{x'\sqrt{2}}{\overline{k^2}\omega}\right\}\right] \left[\Phi\left\{\frac{\lambda\tau_y}{\sqrt{2}}\varrho + \frac{y'\sqrt{2}}{\overline{k^2}\varrho}\right\} + \Phi\left\{\frac{\lambda\tau_y}{\sqrt{2}}\varrho - \frac{y'\sqrt{2}}{\overline{k^2}\varrho}\right\}\right] \quad (24)$$

where

$$\omega = \sqrt{\frac{1}{\lambda^2 \overline{x_k^2}} + \frac{1}{\overline{k^2}}}, \quad \varrho = \sqrt{\frac{1}{\lambda^2 \overline{y_k^2}} + \frac{1}{\overline{k^2}}} \quad (25)$$

Eq 24 gives a sufficiently adequate description of the distribution function for the limiting case $\sqrt{\overline{k^2}} \gg (\lambda\tau_x/2)$, $\sqrt{\overline{k^2}} \gg (\lambda\tau_y/2)$ Another limiting case is presented by a feeble scatter on the compensator, i e $\sqrt{\overline{k^2}} \ll (\lambda\tau_x/2)$ and $\sqrt{\overline{k^2}} \ll (\lambda\tau_y/2)$

As the compensator thickness is decreased, the fluence approximates asymptotically a function $j^0(x, y)$ of the following form

$$j^0(x', y) = j(x', y') - j_1(x', y') \quad (26)$$

where $j(x, y)$ and $j_1(x, y')$ are found from eqs 9, 14 and 15, respectively In the case of $\sqrt{\overline{k^2}} \sim (\lambda\tau_x/2), (\lambda\tau_y/2)$ the function sought will be between the two asymptotics Therefore, it is preferable to use an approximated function, i e a linear superposition of asymptotic solutions, for the practical purposes of calculations in this area

$$j_2(x', y') = \frac{1}{2} j_2^{a}(x', y') + \frac{1}{2} \frac{j_2^{a}(x' = 0, y' = 0)}{j^0(x' = 0, y' = 0)} j_2^0(x', y') \quad (27)$$

Fig 8 illustrates both functions included in eq 27 determined for a compensator with the parameters mentioned The lead compensator thickness t_k is 0 1 mm The value for parameter $\overline{k^2}$ is obtained from a formula similar to eq 16

$$\overline{k^2} = 11\,9 \frac{(D - d_k)^2}{E^2} t_k [4\,29 + \lg t_k] \quad (28)$$

After $j_2(x, y)$ is calculated it remains only to add $j_1(x', y')$ to find the actual fluence $j_k(x', y')$

The total fluence $j_k(x', y')$ for the compensator and foil scatterer appears in Fig 9 The value of j_k at $x' = 0$, $y' = 0$ equals unity This figure also demonstrates experimen-

Substituting foil thickness in g/cm², values of D in cm and E in MeV, we get $\overline{\tau'^2} = 285$ cm²

The projections of the compensator boundaries are found from the equations

$$X_k^1 = 1\,455\frac{\tau_x}{2} - 0\,455\,x', \quad Y_k^1 = 1\,455\frac{\tau_y}{2} - 0\,455\,y'$$

The distribution of electrons subjected to additional scattering influence of the compensator may be determined by means of computation of the fluence $j(x_k, y_k)$ in the compensator plane It is described by an equation similar to 9, the value of d_k being substituted for D The values of γ, $\overline{\tau'^2}$ and δ are changed, accordingly

$$\gamma_k = \frac{d_k + L}{L}, \quad \overline{\tau_k^2} = \overline{\theta}\, d_k^2 = \overline{\tau^2}\frac{d_k^2}{D^2}, \quad \delta_k = \sqrt{\frac{1}{\gamma_k^2 \overline{x'}} + \frac{1}{\overline{\tau_k^2}}} \tag{17}$$

For further convenience, eq 9 is approximated in the ranges of $-(\tau_y/2)$ to $+(\tau_y/2)$ *and of* $-(\tau_x/2)$ *to* $+(\tau_x/2)$ *by a simpler function*

$$j(x_k, y_k) \approx j^a(x_k, y_k) = N_k \exp\left(-\frac{x_k^2}{\overline{x_k^2}} - \frac{y_k^2}{\overline{y_k^2}}\right) \tag{18}$$

Taking into account eqs 17 and 18, the following may be obtained

$$N_k = j(x_k = 0, y_k = 0) = \frac{1}{\gamma_k^2 \delta_k \sqrt{\overline{\tau_k^2}}}\, j_0\, \Phi\{a\gamma_k \delta_k \sqrt{2}\}\, \Phi\left\{\frac{b\gamma_k \sqrt{2}}{\sqrt{\overline{\tau_k^2}}}\right\} \tag{19}$$

The values of $\overline{x_k^2}$ and $\overline{y_k^2}$ are determined by the fluence magnitude at compensator boundaries

$$N_k \exp\left(-\frac{\tau_x^2}{4\overline{x_k^2}}\right) = j\left(x_k = \frac{\tau_x}{2}, y_k = 0\right), \quad N_k \exp\left(-\frac{\tau_y^2}{4\overline{y_k^2}}\right) = j\left(x_k = 0, y_k = \frac{\tau_y}{2}\right) \tag{20}$$

Eqs 19 and 20 yield all the parameters included into the approximate function $j^a(x_k, y_k)$

Introduce symbols

$$\overline{K^2} = \overline{\theta_k^2}(D - d_k)^2 \tag{21}$$

where $\overline{\theta_k^2}$ = mean-square angle of scattering in the compensator

$$\lambda = \frac{D}{d_k} \tag{22}$$

The precise determination of the fluence $j_2(x, y)$ is complicated because this function is expressed by the four-fold integral with respect to the area of the foil scatterer and compensator, which cannot be reduced to elementary functions Therefore, it seems appropriate only to consider an approximate method of calculation

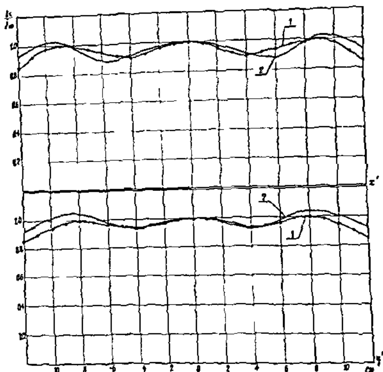


Fig 9 Fluence of electrons in the plane x y' – $j_k(x', y')$ 1—experimental distribution, 2—estimated distribution

a coincidence is characteristic of all compensators It is observed only, *when the* conditions discussed below are met with

Introduce the notion of an 'effective source' which corresponds to the effective area of the compensator equalization Designate the coordinates of the effective source boundaries in x- and y directions as Δ_x and Δ_y, respectively (Fig 6) Then, by analogy with eq 13

$$R_{xt} - T_x = \tau_{xt} = \frac{(a-\Delta_x)(D-d_k)}{d_x}, \quad R'_{yt} - T'_y = \tau'_{yt} = \frac{(b-\Delta_y)(D-d_k)}{d_k} \qquad (29)$$

where τ_{xt} and τ_{yt} are the effective penumbra dimensions and Δ_x and Δ_y the coordinates of the effective source boundaries

Hence,

$$\Delta_x = \frac{d_k}{D-d_k}(R'_{xt} - T'_x) - a, \quad \Delta_y = \frac{d_k}{D-d_k}(R'_{yt} - T'_y) - b \qquad (30)$$

The size of the effective source is mainly determined by the foil scatterer thickness The coincidence of the sizes of the effective and *geometric* penumbra sizes τ' and τ'_t

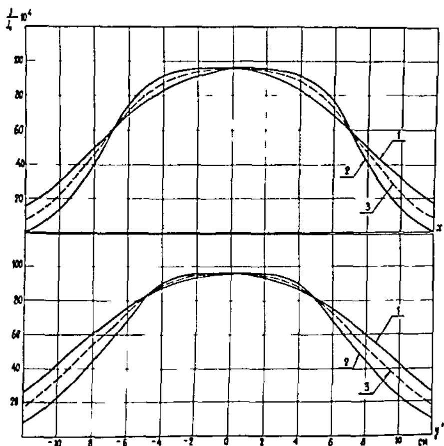


Fig 8 Fluence of electrons perpendicular to the beam axis at the treatment distance

$1 - j_2^{\sigma}(x', y')$ $\quad 2 - \dfrac{j_2^{*}(x'=0, y'=0)}{j_2^{0}(x'=0, y'=0)} j_2^{0}(x', y')$ $\quad 3 - j_2(x', y)$

tal data on the distribution of the formed electron beam without tubes and diaphragms 3, 4, 5 Both distributions appear to be in satisfactory agreement The error is slightly increased due to air scattering, as the thickness of the foils and compensators are decreased For instance, when foils, equivalent in scattering effect to that of a 0 5 mm-thick Al foil, $D \approx 100$ cm, are used error may be in excess of 15 per cent from the maximum value of the fluence $j_k(x', y')$ However, the use of the discussed approximation may also be of advantage in the evaluation of a specific compensator in the case of *thin foil application*

It is apparent from Figs 7, 8 and 9 that the effective area of the compensator equalization is smaller than the geometric area found from eq 13 To specify the coordinate of the penumbra boundary, R_y along y'-axis is 15 cm whereas the effective compensation boundary R'_{yf} is 12 cm long Assume the value of R'_f to be the coordinates of points, at which the fluence $j_k(x', y')$ is 90 per cent from maximum (This corresponds to a maximum dose variation of 10 per cent) Along the x'-axis, the values of R'_x and R'_{xf} nearly coincide $R'_x = 11$ 6 cm and $R'_{xf} = 12$ cm However, such

(3) The size of the area where $j_1(x', y') = 0$ should not exceed that of the region where the dose variation $j_2(x', y')$ equals 10 per cent This is the case at

$$e^{-(T'^2/\overline{\tau^2})} = 0\ 91 \tag{34}$$

Otherwise, the total fluence $j_k(x', y')$ at the boundary of the shadow will exceed that at the centre $j_k(x'=0, y'=0)$ by more than 10 per cent As a first approximation, the value of T' may be taken to be the same in all directions and equal to T_x, then compensator sizes along x_k- and y_k axes may be obtained from eq 13

$$\frac{\tau_x}{2} = \frac{T'-a}{D} d_k + a, \quad \frac{\tau_y}{2} = \frac{T'-b}{D} d_k + b \tag{35}$$

A rectangular compensator with such dimensions ensures a sufficiently adequate uniformity of distribution along x'- and y'-axes However, 'sags' at the shadow boundaries in directions, corresponding to the source diagonals, may be greater than allowed The beam form may be improved by application of an octagonal compensator with the same τ_x and τ_y sizes and a less dimension along the vector parallel to the source diagonal The latter size may be found from eq 35 by substituting $\sqrt{a^2+b^2}$ for a Still better uniformity may be attained by the use of an oval compensator

The conditions and formulas described make possible the choice of the thickness of the fixed scattering foil as well as the sizes and formula for the compensator and the scatterer to compensator distance for the field with a given dimension 2A

By way of illustration, consider the computation of a compensator for a field with a diameter $2A = 23$ cm

According to eq 32, at k 0 6

$$\sqrt{\overline{\tau^2}} = \frac{A}{0\ 71} = 16\ 2 \text{ cm}$$

For electron energy $E = 20$ MeV, the above value of $\overline{\tau^2}$ may be achieved by application of a lead foil with a thickness $t = 0\ 37$ g/cm^2 or 0 33 mm Further, the following is obtained on the basis of eq 34

$$T' = 0\ 307\sqrt{\overline{\tau^2}} = 5\ 0 \text{ cm}$$

After substitution of $D = 80$ cm, $2a = 3$ cm, $A = R'_x = 11\ 5$ cm and $T_x = 5\ 0$ cm in eq 31,

$$d_k = 25 \text{ cm}$$

Compensator sizes τ_x and τ_y are found from eq 35

$$\tau_x = 5\ 2 \text{ cm}, \quad \tau_y = 6\ 5 \text{ cm}$$

When the basic parameters of the compensator and foil are available, compensator thickness t_k may be determined The calculation procedure for thickness determination is as follows

may be attained by changing the foil thickness and, therefore, parameter $\sqrt{\overline{\tau^2}}$ Maximum therapeutic area is available only, when the sizes of the geometric and effective sources coincide This condition cannot be met with for all directions in the x'y'-plane simultaneously, since the 'source' is not axially symmetric For instance, in this specific case, the source is rectangular in form measuring $2a \times 2b$ and electron distribution in xy-plane is described by eq 8 It is desirable to choose such a size of the effective source that it should coincide with the minimal size of the geometric source Since the size of the entrance diaphragm aperture is minimal along the x-axis in the given system of beam forming

$$\Delta_{x\,max} \approx -a$$

Substituting the value of $\Delta_{x\,max}$ in eq 30, it is found that

$$d_x = \frac{2aD}{R'_x - T'_x + 2a} \tag{31}$$

Eq 31 determines the maximum foil scatterer-to-compensator distance, at which a therapeutic field with the diameter of $2A \approx 2R'_x$ is formed

Previously it has been found that the following requirements should be met with to provide an effective equalizing of the therapeutic field

(1) The thickness of the foil scatterers should be such as to ensure that the fluence at the boundaries of the desired therapeutic field is within 0 5–0 7 of the value $j(x = 0, y' = 0)$ when no compensator is used The foil thickness may be found with a satisfactory degree of accuracy from the following equation

$$\frac{j(x' = A, y' = 0)}{j(x' = 0, y' = 0)} = e^{-(A^2/\overline{\tau'^2})} = k, \quad 0\,5 \leqslant k \leqslant 0\,7 \tag{32}$$

Eq 32 is derived from eq 9 at $\overline{\tau'^2} \gg \gamma^2 \overline{x^2}$

Practical experience shows optimal equalization to be achieved at $k = 0\,6$ In this case the boundary of the uniform area R'_{xf} coincides with the geometric boundary of the compensator effect R'_x

Formulas, similar to eq 16, including a relationship between foil thickness t and the value of $\overline{\tau'^2}$ for two other materials are given below

For aluminium,

$$\overline{\tau^2} = 2\,44 \frac{D^2}{E^2} t[4\,11 + \lg t] \tag{33}$$

For copper,

$$\overline{\tau^2} = 4\,92 \frac{D^2}{E^2} t[4\,20 + \lg t]$$

(2) The limits of the true equalized area of the compensator R_f should be outside the boundaries of the required therapeutic field $R'_f \geqslant A$

This condition implies that the fluence magnitude at the therapeutic field centre should be equal to the maximum values near its boundaries. Hence, the compensator is supposed to reduce the fluence at the field centre to $j_k(x'=x'_{max}, y'=0)$. Both this value and coordinate x_{max} may be found by the step-by step approximation method on the basis of eqs 14 and 27. Assuming $j_2(x'=0, y'=0)$ to be equal to the maximum of $j_1(x', y'=0)$ and calculating $j_k(x', y'=0)$ within the penumbra area, coordinate x_{max} and the magnitude of $j_k(x'=x'_{max}, y'=0)$ is found. Setting $j_2(x'=0, y'=0)$ to be equal to the found value of $j_k(x'=x'_{max}, y'=0)$ and reiterating the calculations, a more precise value of $j_k(x'=x'_{max}, y'=0)$ is obtained. After reiterating the operation the required number of times, the value $j_2(x'=0, y'=0)$ is obtained to the desired accuracy.

Introduce a coefficient of the compensator reduction of the fluence at the therapeutic field centre $(x'=0, y'=0)$

$$\varepsilon=\frac{j_2(x'=0, y'=0)}{j(x'=0, y'=0)} \tag{36}$$

From eqs 24 and 27 it follows that

$$j_2(x'=0, y'=0)=\frac{N_k}{\overline{k}\,\lambda^2\omega\varrho}\,\Phi\left\{\frac{\lambda\tau_x}{\sqrt{2}}\omega\right\}\Phi\left\{\frac{\lambda\tau_y}{\sqrt{2}}\varrho\right\} \tag{37}$$

When the required reduction is found from eqs 36 and 37, the coefficient including compensator thickness is easy to obtain

$$\overline{k}^2=\frac{F}{\varepsilon\omega\varrho}\,\Phi\left\{\frac{\lambda\tau_x}{\sqrt{2}}\omega\right\}\Phi\left\{\frac{\lambda\tau_y}{\sqrt{2}}\varrho\right\} \tag{38}$$

where

$$F=\frac{1}{\lambda^2}\frac{\gamma}{\gamma_k}\sqrt{\frac{\overline{\tau^2}+\gamma^2\overline{x^2}}{\overline{\tau_k^2}+\gamma_k^2\overline{x^2}}}\,\frac{\Phi\{a\gamma_k\delta_k\sqrt{2}\}}{\Phi\{a\gamma\delta\sqrt{2}\}}\,\frac{\Phi\left\{\frac{b\gamma_k\sqrt{2}}{\sqrt{\overline{\tau_k^2}}}\right\}}{\Phi\left\{\frac{b\gamma\sqrt{2}}{\sqrt{\overline{\tau^2}}}\right\}} \tag{39}$$

Eq 38 may be solved with respect to $\overline{k}^2$ by the step by step approximation method or graphically.

The relationship between $\overline{k}^2$ and compensator thickness t_k is expressed by the following equations, similar to eq 16.

For aluminium

$$\overline{k}^2=2.44\frac{(D-d_k)^2}{E^2}t_k[4.11+\lg t_k] \tag{40}$$

for copper

$$\overline{k}^2=4.92\frac{(D-d_k)^2}{E^2}t_k[4.20+\lg t_k]$$

for lead

$$\overline{k}^2=11.9\frac{(D-d_k)^2}{E^2}t_k[4.29+\lg t_k]$$

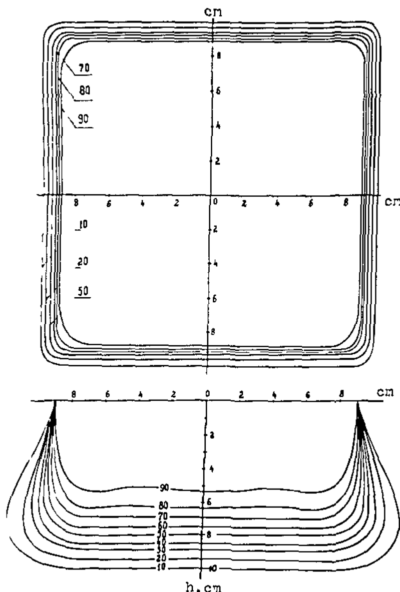


Fig 10 Isodose curves in the plane perpendicular to beam axis at depth of 2 cm in a water phantom and in the plane $y=0$ 0 35 g/cm²-thick lead scattering foil, 0 11 g/cm²-thick lead compensator, $\tau_x = 5\ 2$ cm, $\tau_y = 6\ 0$ cm Field 18 cm × 18 cm Electron energy 20 MeV

An indispensable condition of the uniform distribution of electrons over the surface of the medium along the x'-axis is the form

$$j_2(x'=0, y'=0) = j_1(x'=x'_{max}, y'=0) + j_2(x'=x'_{max}, y'=0)$$

A similar condition should also be met for the y'-axis

$$j_2(x'=0, y'=0) = j_1(x'=0, y'=y'_{max}) + j_2(x'=0, y'=y'_{max})$$

where x'_{max}, y'_{max} are coordinates corresponding to maximum fluences $j_k(x', y=0)$ and $j_k(x'=0, y')$ (Fig. 9)

According to eq 31, the maximum size of effective penumbra area $\tau'_{xt} = \tau'_x$ is determined by the distance d_x However, once d_x is selected, also compensators designed by fields of smaller size may be used to advantage The equalized area of such compensators may be found by means of eqs 14, 15, 24, 26 and 27

SUMMARY

The technique of forming electron beams by one scattering foil and one compensating foil is discussed This method provides a means for producing large-size uniform dose distributions with much smaller losses in dose rate as compared with conventional beam forming by one foil Moreover, the energy losses involved in this process and the background of concomitant bremsstrahlung are much less A technique of calculation to determine approximate parameters of the compensating foils is described

ZUSAMMENFASSUNG

Die Technik, Elektronenstrahlen unter Anwendung einer Streufolie und einer Kompensationsfolie zu formen, wird diskutiert Die Methode bietet einen Weg, grossflächige einheitliche Dosisverteilungen mit wesentlich geringeren Verlusten der Dosisleistung verglichen mit denen bei der konventionellen Formung mit einer Fol [illegible]
sind die bei diesem P [illegible]
tigen Bremsstrahlung [illegible]
Parameter der Kompensationsfolien zu berechnen, beschrieben

RESUMÉ

Les auteurs étudient la technique de production de faisceaux d electrons par un ecran diffusant et un écran compensateur Cette [illegible]
distributions de doses uniformes de gr [illegible]
inférieures à celles que donne la clas [illegible]
plus, les pertes d'énergie impliquées par cette technique et la Bremsstrahlung concomitante sont bien moindres Les auteurs decrivent une technique de calcul pour déterminer les paramètres approximatifs des écrans compensateurs

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Calculations show that for compensators and foils, which meet the above conditions at $k=0\ 6$, the magnitude of ε is near 0 73 Substituting $\varepsilon=0\ 73$ in eq 38, and on the basis of a graph of functions in the left and right parts of the equation for this case of a compensator with $\tau_x=5\ 2$ cm and $\tau_y=6\ 5$ cm

$$\overline{R}^2 \approx 27 \text{ cm}^2$$

Further, the compensator foil is found with the aid of eq 40

$$t_k \approx 0\ 09 \text{ g/cm}^2 \text{ Pb}$$

Following the estimation of compensator and foil parameters, the latter are further improved by experiments The following procedure may be suggested for this purpose

The first requirement is an adequate choice of the thickness of the fixed scattering foil It follows from eq 32 that the width of the scattered non-collimated beam in x'y'-plane at 0 6 of the maximum fluence value should equal 2A Then, the compensator centre position is determined The choice of the centre position is confirmed by the criterion of symmetry of electron distribution along x - and y -axes Then the thickness of compensator—t_k—is selected The magnitude of t_k is optimal, when the fluences near the boundary of compensation and at the field centre coincide along x'-axis, which corresponds to the minimal size of the source If, then, the fluence near the field boundary, in another direction, is insufficient, the relevant size of the compensator has to be decreased In the case of adequately chosen dimensions of the compensator, electron distribution over the therapeutic field is approximately axially symmetric

Estimation of the compensator and foil scatterer using the methods mentioned demonstrated that a field of 23 cm in diameter (dose variation 10 %) may be formed using a 0 35 g/cm^2 thick lead scattering foil and 0 11 g/cm^2 thick lead compensator with $\tau_x-5\ 2$ cm and $\tau_y=6\ 0$ cm This demonstrates that the proposed methods of calculation offer a satisfactory accuracy in the determination of the compensator and foil scatterer parameters which ensure the formation of uniform therapeutic fields of desired sizes

In conclusion, it may be pointed out that the compensator design, meeting the conditions in eqs 31 and 34, is not the only possible solution For instance, the version, described at the beginning of this report was developed at

$$e^{(T^2/\overline{r^2})} = 0\ 93, \quad k=0\ 7, \quad d_k \quad 25 \text{ cm}$$

The field uniformity near boundaries x T or y =T may be improved by decreasing the shadow area T while the true equalized area R_f is somewhat extended, when coefficient k is increased

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ANTI-OESTROGEN THERAPY OF ADVANCED MAMMARY CARCINOMA

HELENA WESTERBERG, B NORDENSKJÖLD, A DE SCHRYVER and G NOTTER

Anti oestrogens have activity against experimental and human mammary ca cinoma HERBST et coll (1964) administered clomiphene to patients with advanc breast tumours and reported 6 responders Subsequently COLE et coll (1971, 197 WARD (1973) and BREWIN (1973) observed that a high proportion of their patie responded to the anti oestrogen tamoxifen (ICI 46 474—Nolvadex, Imperial Chemi Industries, England) Similarly the EORTC Breast Cancer Group (1972) and BLO & BOESEN (1974) established that the anti-oestrogen Nafoxidine (Upjohn) was act against advanced mammary carcinoma These favourable experiences promp trial with tamoxifen at Radiumhemmet, Stockholm, and at the Department Radiation Therapy, Gothenburg

Material and Methods

The material consisted of 89 postmenopausal women, all with measurable tumo mainly primary inoperable or locally recurrent carcinoma Forty-seven were o 70 years old, 34 were between 56 and 69, and 8 patients were 55 years old or youn The main tumour localizations appear in Table 1 Patients with osseous metast only were excluded because of the difficulty in evaluating and measuring a remiss

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Table 2

Number of patients with response

Response category	Response at			
	2 months	6 months	12 months	18 months
1	6	9	10	4
2	32	29	18	9
3	19	8	5	—
4	32	42	44	28
Total	89	88	77	41

at four different time points are given in Table 2 After two months of therapy 38 out of 89 patients (43 per cent) had responded In the following 4 to 5 months another 6 patients responded with complete or incomplete remissions, bringing the total response rate to 49 per cent

Eighty-eight patients were observed for more than 6 months (Table 2) The number of patients with complete and incomplete remission at 2 and at 6 months was 38/88 (42 per cent) However, the fraction of patients in complete remission had increased from 6 to 10 per cent Thirty one patients were classified as non responders at 2 months, as compared to 42 patients at 6 months

Seventy seven patients were followed for more than one year Twenty-eight of these (35 per cent) were still responding to tamoxifen therapy at 12 months (Table 2) Forty one patients have been followed for more than 18 months (Table 2) Thirteen (32 per cent) were still responding to treatment at the end of this time Twelve patients began treatment 22 months ago Six were responders, one is still in complete remission at 22 months, five had complete and partial remissions of 6 to 15 months duration (mean 12 months) Among the 6 non responders, 5 are dead, while one is still alive with progressive disease (Out of 12 responders who relapsed on 40 mg daily, 4 experienced another period of remission on 80 mg daily) Six patients had complete remission at 2 months, 9 patients at 6 months and 10 patients at 12 months

Forty six patients without previous endocrine therapy were compared to 43 patients previously treated with hormones or endocrine ablative surgery (Table 3) The results were more favourable in patients without previous endocrine therapy, 30 out of 46 responded (65 per cent) as compared to 14 out of 43 (32 per cent) in the latter group Therapy response was also correlated to age The response rates in the age groups 56 to 69 years and those over 70 years were exactly the same Eight patients whose age was less than 55 years failed to respond to tamoxifen treatment

In 4 patients progression was due to development of osseous metastases, while the soft tissue disease was still under control Differences in hormone sensitivity of metastases in various tissues to oestrogen therapy has also been reported by Stoll (1973)

Table 1

Dominant sites of disease

Dominant site	No of patients
Primary mammary tumours	22
Metastases	
Cutaneous	29
Lymph node	17
Pulmonary	9
Liver	1
Generalized	11
Total	89

objectively Forty-three of the 89 patients had received previous endocrine therapy such as oophorectomy or addition of androgens, corticosteroids or oestrogens The remainder, 46 patients, had received no such treatment

Tamoxifen is the transisomer of 1 (p-beta-dimethyl-amino ethoxyphenyl) 1,2 diphenyl-but-1-ene The drug was supplied by the Imperial Chemical Industries, England The standard dose was 20 mg twice daily orally Exceptions (20–240 mg daily) are specified in the following The total doses varied between 1 400 mg/35 days and 36 600 mg/990 days

Evaluation Primary tumours, nodal and cutaneous metastases were measured using a caliper and frequently photographed The tumours of the 9 patients with lung metastases (Table 1) were evaluated by measurement of their diameters on chest films One patient (non-responder) with liver metastasis was estimated by measurements of palpable liver size, serum bilirubin and serum alkaline phosphatase The following response categories were used (1) Complete remission, i e disappearance of all apparent tumour, (2) partial remission, i e more than 50 per cent reduction in the products of the two largest diameters of the lesions, (3) stationary disease, and (4) progression, i e more than 50 per cent increase in the sum of the products of the diameters of lesions These symbols are used in the tables to indicate response categories The patients were generally evaluated at one week, 3 weeks and then every 4 to 6 weeks after the beginning of treatment The patients were examined by chest films and isotope bone-scan at the beginning of treatment and at every 6 to 12 months To obtain the data in Table 2 the tumour diameters at 2, 6, 12 and 18 months, respectively, were compared with the diameters at the start of treatment

Results

The value of endocrine therapy depends on several factors such as extent of response, duration of response, and severity and duration of side effects The response

binding of anti oestrogens to the oestrogen receptor (HÄHNEL et coll 1973) To compete with endogeneous oestrogen, tamoxifen therefore has to be administered in excess In a high fraction of patients the standard dose (40 mg daily) was evidently sufficient to overcome naturally occurring oestrogen In most patients 40 mg daily was tolerated without side effects In several patients with progressing tumours this dose could be increased to 80 mg and in one patient to 200 to 240 mg daily for 2 months without obvious side effects Taken together, the limited side effects, the reinduction of response observed after increase of dose, and the known difficulty to overcome oestradiol with anti oestrogen, argue for the use of the highest doses tolerated

Addition of oestrogen is the established therapy of choice in older patients The results with tamoxifen suggest that inhibition of oestrogen activity may be as efficient as addition of oestrogen in elderly patients Forty five out of 81 patients older than 55 years responded to tamoxifen (55 per cent) Others have reported 20 to 80 per cent complete or partial response The figures vary with patient selection and definitions of response, but are generally similar to those obtained with oestrogen therapy (STOLL) With oestrogen therapy the response rate increases with increasing time after menopause (STOLL) No correlation between age and the therapeutic effect of tamoxifen was observed in patients over 55 years of age The effect of tamoxifen in postmenopausal patients may be correlated to the fact that also elderly patients may excrete significant amounts of oestrogen (NISSEN MEYER & SANNER 1963)

Since the side effects were few and the response similar to that of oestrogens, androgens and corticosteroids, it is suggested that tamoxifen should be used as the first choice in endocrine therapy of soft tissue mammary carcinomas in postmenopausal women

SUMMARY

Forty mg daily of tamoxifen (Nolvadex) was administered orall ... 89

... are less

ZUSAMMENFASSUNG

Täglich 40 mg Tamoxifen (Nolvadex) wurde oral 89 Patienten mit fortgeschrittenen Weichgewebe Mammakarzinomen verabfolgt Nach 2 Monaten hatten 43 Prozent der Patienten reagiert Nach 6 12 und 18 Monaten reagierten immer noch 42, 35 und 32 Prozent gegenüber der Therapie Die Nebenwirkungen waren ...
hauptsächliche Östrogen ...
peutische Wirkung
geringer

Table 3

Number of patients with response, related to previous endocrine therapy

Response category	Previous endocrine therapy	No previous endocrine therapy	All patients
1 and 2	14	30	44
3 and 4	29	16	45
Total	43	46	89

Few side effects occurred during tamoxifen therapy Twenty patients suffered from moderate to severe fatigue This was almost exclusively a complaint among elderly patients It seems obvious that the fatigue was the result of tamoxifen therapy, rather than the effect of the disease, since the fatigue disappeared in several patients after discontinuation of therapy A weight gain of 3 to 8 kg occurred in 10 patients Oestrogen dependent side effects, i e oedema, hypertension, vaginal bleeding, were minimal Only one patient developed flushes and nausea Two patients demonstrated some hirsutism, and one patient without axillary hair before therapy developed such hair after initiation of therapy A moderate hair loss was demonstrated in 3 patients These effects were considered as indicating a weak androgen activity One responder had deep vein thrombosis which disappeared after a few months of anticoagulant therapy This patient then remained well in spite of continued tamoxifen therapy Cutaneous rash and dry skin developed in 3 patients Nausea was rare (2 patients) Two patients developed moderate diarrhoea No signs of bone marrow depression or liver toxicity occurred

In several patients, who did not respond, or relapsed at 40 mg, the daily dose was increased to 80 mg In one non-responding patient, the dose was gradually increased to 240 mg daily without obvious side effects but also without therapeutic effect on the cutaneous metastases

Discussion

The molecular mechanism behind regression of mammary carcinoma after endocrine therapy is poorly understood (STOLL) The presence of oestrogen receptors in mammary carcinomas responding to endocrine therapy and the therapeutic effect of procedures that alter the oestrogen level, suggest that adequate oestrogen levels may be important for optimum tumour cell replication (MCGUIRE et coll 1974) Oestrogen activity may be decreased by oophorectomy, adrenalectomy or irradiation to the ovaries Tamoxifen binds to the oestrogen receptor (JORDAN & KOERNER 1975) and is able to block oestrogen activity (JORDAN & KOERNER, to be published)

The binding of oestradiol to the oestrogen receptor is much stronger than the

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SCANNING ELECTRON MICROSCOPY OF CELLS IN THE LYMPH OF THE HUMAN THORACIC DUCT IN ADVANCED MALIGNANCIES

O DAHLBÄCK, H DENCKER, C H HÅKANSSON, L G LINDBERG and C v MECKLENBURG

It is a well established fact that most of the immunoactive lymphocytes must pass the thoracic duct Therapeutic use of lymphocytes has been practised in the treatment of malignancies (YONEMOTO & TERASAKI 1972) In cats SUGIMURA et coll (1973) found that lymphocytes dominated up to 85 per cent of all cells in the thoracic lymph Drainage of the thoracic duct has been used in man in the treatment of hepatitis and pancreatitis and immunosuppressive results have been obtained in renal transplantation (BARTOS & BRZEK 1973, BRZEK & BARTOS 1969, TILNEY & MURRAY 1967) As only few investigations of thoracic duct cells have appeared from patients with advanced carcinomas, scanning electron microscopy of such cells was performed and the result is now reported

Material and Methods

The investigation comprised cells from 30 patients, 19 women and one man with mammary carcinoma, 3 males with carcinoma of the urinary bladder, 4 males and 2 women with pulmonary carcinoma, and one patient with malignant melanoma

This investigation was supported by grants from B Kamprad s Foundation Submitted for publication 15 January 1976

RÉSUMÉ

Quarante mg de tamoxifen (Nolvadex) ont été administrés quotidiennement par voie orale à 89 malades atteintes de cancer avancé des parties molles du sein Au bout de deux mois, 43 pour cent des malades ont répondu à ce traitement Au bout de 6, 12 et 18 mois, 42, 35 et 32 pour cent respectivement, répondaient encore au traitement Les effets secondaires sont limités, la fatigue étant le symptome le plus fréquent On n'a pas observé d effet secondaire dépendant des oestrogènes L'effet thérapeutique du tamoxifen est semblable à celui des oestrogènes mais ses effets secondaires sont moindres

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Fig 3 Normal erythrocyte together with an echinocyte and probably an achantocyte (6 000 ×)

with lung metastases large cells with rough surfaces were observed, some of them in close association with small lymphocytes These cells were regarded as being malignant (*Fig 1*) *Cells* obtained from a patient with a metastasis in the left axilla *confirmed by fine needle* aspiration are illustrated in Figs 2 to 5 The metastasis measured 3 *cm* × 3 *cm* × 3 cm at the time of the collection of the cells Many *erythrocytes and leucocytes* with pseudopodic formation indicate their ability to migrate (*Fig 2*) *The round* structures in the figure are regarded as small lymphocytes A bridge like connection bet [illegible]

[illegible] appears in the figure together with an echinocyte and a cell considered to be *an acanthocyte* This term was introduced by Bessis (1973) *to* indicate the shape, and not *to assume a supposed* β lipoproteinaemia Two different cells are displayed in Fig 4 The *front* cell was regarded as a spherocyte, while the upper one was assumed to be a macrophage *It* seems also possible, however, that it is an aggregate of lymphocytes with uropodes, covered by a sheet of a protein like structure Even though heparin was used in the preparation, it cannot be excluded that fibrin remnants or lipoproteins might cover the cell membranes A magnification of a lymphocyte is illustrated in *Fig 5 Its* migratory capacity is clearly demonstrated by the small 'foot' in the front and the typical uropode

Without change *of therapy*, the metastasis in the left axilla disappeared and no malignant cells were found at *repeated fine* needle biopsy Whether this effect was caused by the drainage of the thoracic lymph during several days or by the ligation of the duct itself is not clear

Two erythrocytes *and* 5 small lymphocytes appear in Fig 6 The large cell *in the* figure is difficult to *identify, possibly it represents* a large lymphocyte However, many lymphocytes are *collected* around the cell and it might be *suggested that it is* a

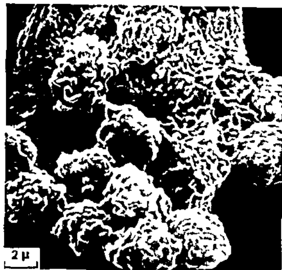




Fig 1

Fig 2

Fig 1 Connection between lymphocytes and an abnormal cell, considered to be malignant (6 000 ×)

Fig 2 Several erythrocytes and some lymphocytes between them To the right a leucocyte has a bridge-like connection to an erythrocyte (2 400 ×)

Collection of cells An incision was made under local anaesthesia lateral to the sternal tendon of the left sternocleidomastoid muscle and dissection was performed along the jugular vein down to the junction between the subclavian vein and the thoracic duct The entrance of the duct into the vein was ligated in order to avoid any backflow of blood A polyethylene catheter was inserted into the duct and ligatures were placed around the duct with the catheter in place The skin was then sutured and the other end of the catheter was drained into a plastic bottle

Scanning electron microscopy Five ml of lymph was collected from the patients in 5 ml physiologic NaCl in heparinized test tubes The cells were sedimented by centrifugation and fixed in glutaraldehyde 2 5 % in 0 2-M Caccodylate-buffer for one hour After sedimentation the specimen was rinsed several times in pure buffer, followed by further rinsing in distilled water After sedimentation, one or two drops of the rinsed cell suspension were placed on a clean, circular cover slide and dried in an incubator at 37°C Some specimens were dried according to the critical-point method with carbon dioxide for comparison (ANDERSSON 1951) All specimens were coated in a vacuum evaporator with gold-palladium and examined in a Cambridge Stereoscan Mark II A scanning electron microscope

Results

Patients with mammary carcinoma In patients with skin, lymph node and skeletal metastases, no cells in the thoracic lymph were considered malignant In patients

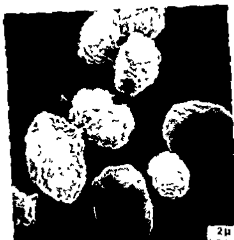


Fig 7



Fig 8



Fig 9

Fig 7 Several lymphocytes and 2 erythrocytes to the right A large cell similar to the one seen in Fig 6 (6 000 ×)

Fig. 8 Lymphocytes and erythrocytes with a large cell similar to those in Figs 6, 7 Connection to two of the erythrocytes (6 000 ×)

Fig 9 A lymphocyte, a spherocyte and a spheroechinocyte with small spiny projections and several erythrocytes (6 000 ×)

Normal erythrocytes (discocytes), erythrocytes of different shapes, and two spherocytes at different stages are illustrated in Fig 9 (from another patient) A small lymphocyte appears in the upper part of the figure Fig 10 (same patient) demonstrates one lymphocyte with the rest of the uropode protrusion to the right The other cells belong to the erythrocytic series (spherostomatocyte-transformation), a ball-like cell with a little cup-shaped impression may be observed in the upper part of the figure Two lymphocytes lying closely associated together are observed in the middle of Fig 11 These lymphocytes protrude towards erythrocytes The rest of the cells in the figure are erythrocytes of different shapes, from discocytes to echinocytes I to II A cup-shaped or 'helmet' erythrocyte may be faintly observed in the upper part of the figure



Fig. 4



Fig. 5



Fig 6

Fig 4 Spherocyte in the front and possibly a macrophage (or a conglomerate of lymphocytes) (6 000 ×)

Fig 5 A lymphocyte with its uropode directed backwards (10 000 × .)

Fig 6 Five small lymphocytes and possibly a large lymphocyte or a malignant cell, 1 erythrocyte to the left. (6 000 ×)

malignant cell with attacking immunoactive lymphocytes, as in Fig 7. The cell in the upper part of Fig 8 (from the same patient) seems to have the same appearance. Threads or bridges between lymphocytes and erythrocytes were considered to exist. The function of this connection is not known. The crippled cell in the middle of Fig. 8 belongs to the erythrocytic series; it is unclear if it represents an artefact or if the appearance is an effect of the treatment.



Fig 13



Fig 14



Fig 15

Fig 13 Lymphocytes with slender projections sometimes directed towards the erythrocytes (6 000 ×)

Fig 14 Collection of small lymphocytes above a cell considered to be malignant (From a patient with pulmonary carcinoma) (1 200 ×)

Fig 15 Abnormal cell considered as malignant (From a patient with a pulmonary squamous cell carcinoma) (6 000 ×)

carcinoma and lung metastases and from patients with pulmonary carcinoma The shape of the erythrocytes, as well as the behaviour of the lymphocytes in patients with malignant tumours are of interest (cf MEISELS 1969, NIEBURGS 1974)

The red blood cells vary in shape with the osmotic pressure (PONDER 1948) Recently BESSIS has given a survey over the ultrastructural appearances of normal and pathologic conditions of the blood cells Many of the conditions he described have occurred in the present material of thoracic lymph cells Even small spicules could be detected

Different stages of the transformation of discocyte to echinocyte were observed, e g in stage I a biconcave cell with irregular contours (Fig 12, upper part, and Fig 13 lower part) The cell in the upper right corner of Fig 11 also belongs to this type In stage II real spicules appear on the flat cell and in stage III well developed spicules over the entire round cell (Fig 3) A further step is the transformation to sphero-echinocytes which have globe like projections (Fig 9) Extrins c fact - - cause of th

bar



Fig 10



Fig 11



Fig 12

Fig 10 Erythrocytes and a lymphocyte with its uropode pointed to the right (6 000 ×)

Fig 11 Two lymphocytes and several erythrocytes The lymphocytes have projections towards the erythrocytes (6 000 ×)

Fig 12 Several lymphocytes close together, and some erythrocytes (6 000 ×)

Patients with carcinoma of the urinary bladder (Figs 12, 13) No malignant cells were found A large number of small lymphocytes were always present, many of them with protrusions towards erythrocytes of more or less pathologic shape (Fig 13)

Patients with pulmonary carcinoma Cells considered to be malignant were found in the lymph In Fig 14 several small lymphocytes appear, covering a big cell, which was considered as an immunologic reaction Another cell (Fig 15) with abnormal appearance is also probably malignant The size, the finger-like protrusions and the uncommon shape of the cell were considered as evidence of malignancy In other aspects the findings in these patients were similar to those in patients with other types of carcinoma

Discussion

Only few malignant cells were observed in the lymph of the thoracic duct The cells which were considered as malignant were collected from patients with mammary

ZUSAMMENFASSUNG

Bei der Scanning-Elektronen-Mikroskopie der Zellen der Lymphe vom Ductus thoracicus, die durch Kannulation der Patienten mit malignen Tumoren verschiedener Typen gesammelt worden war, wurden Lymphozyten und rote Blutzellen, aber nur wenige maligne Zellen beobachet Letztere kamen von Patienten mit Lungenkarzinomen und Mammakarzinomen mit Lungenmetastasen Verschiedene abnormale Formen der roten Blutzellen wurden gefunden, möglicherweise durch aussere Faktoren wie verabfolgte Pharmaka oder abnormale Metaboliten durch die maligne Erkrankung verursacht Die Lymphozyten wiesen kein pathologisches Bild auf, schienen jedoch als aktive immunologische Zellen gegen den malignen Zellen in der Thorax-Lymphe aufzutreten

RÉSUMÉ

La microscopie électronique à balayage des cellules de la lymphe du canal thoracique, prélevée par cathétérisme sur des malades atteints de tumeur maligne de différents types a montre des lymphocytes et des globules rouges mais très peu de cellules malignes Ces dernières ont été trouvées chez des malades atteints de cancer du poumon et de cancer du sein avec métastases pulmonaires On a constaté de différentes formes anormales de ces globules rouges sanguins, vraisemblablement dues à des facteurs extrinsèques tels que les médicaments administrés ou les métabolites anormaux provenant de l'affection maligne Les lymphocytes n'avaient pas une forme pathologique constante mais paraissaient se comporter comme des cellules immunologiques actives contre les cellules malignes dans la lymphe thoracique

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which may provoke the transformation are non-polar or anionic amphiphilic substances (DEUTICKE 1968) Normal plasma may have an echinocytogenic factor (FEO 1972) It has been suggested that this factor is lysolecithin, and that the acting enzyme may be lecithin-cholesterol-acyl transferase (RAZ et coll 1969) NAKAO et coll (1962) proposed that echinocyte-transformation may be caused by intrinsic factors, and they relate the transformation to the content of ATP in the cells If the cells were deprived of ATP the disc-sphere shape changed

A relationship between the ATP-content and the calcium content of the cell was established by WEED et coll (1969) Furthermore, HARADIN et coll (1969) and LACELLE (1969) demonstrated that blood cells change their shape in relation to the content of ATP within the cells Pleural effusion contains a large number of crenated red cells Aging of the cells with loss of membrane-permeability seems to contribute to this phenomenon In the present cases it may be possible that cytostatic or other drugs given to the patients were echinocytogenic, but it is also possible that the malignant disease itself acted as an echinocytogenic factor SCHWARTZ & MOTTO (1949) have reported an echinocyte-like cell in carcinoma of the stomach, a burr' cell Acanthocytes differ from echinocytes (KAYDEN & BESSIS 1970, WEED & BESSIS 1973) Apart from the fact that they appear in hereditary $\alpha\ \beta$ lipoproteinaemia, they occur in vivo in certain diseases, after injection of heparin and when exposed to lipoprotein lipase (DEVRIES et coll 1960) Other forms of red blood cells are the triconcave cells (knizocyte, Fig 9) and several other malformated cells For the time being it is not possible to attribute the appearances to artefacts, to medical treatment or to the malignant disease itself The cells of the lymph were dominated by lymphocytes with the typical appearance of small lymphocytes, size 6 to 9 μ, large lymphocytes, size 9 to 15 μ (BESSIS) No experiments to distinguish between B and T-lymphocytes by the rosette formation method were performed

The rounded anterior part of a lymphocyte with filaments and the posterior part with the uropode and filaments indicating its migratory capacity appear in Fig 5

Lymphocytes with immunologic activity seem to be illustrated in Fig 14 Hitherto scanning electron microscopy of malignant cells has not given much information of value, probably due to the difficulties in demonstrating the same cell with both this technique and the light microscopy

SUMMARY

At scanning electron microscopy of cells from the lymph of the thoracic duct collected by cannulation of patients with malignant tumours of different types lymphocytes and red blood cells were found but few malignant cells The latter came from patients with pulmonary carcinoma and mammary carcinoma with lung metastases Various abnormal shapes of the red blood cells were observed possibly due to extrinsic factors such as administered drugs or abnormal metabolites from the malignant disease The lymphocytes had no consistent pathologic shape but appeared to act as immunologic active cells against the malignant cells in the thoracic lymph

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EFFECTS ON THE CARDIOVASCULAR SYSTEM OF IRRADIATION FOR MALIGNANT LYMPHOMA

L E LARSSON, J LINDAHL and B UNSGAARD

Complications from the cardiovascular system in connection with irradiation of malignant tumours were observed by COUTARD & LAVEDAN (1922) and have since then been repeatedly reported (LEACH 1943, HARTWEG 1960, JONES & WEDGWOOD 1960) The interest has been focused mainly on the heart and arrhythmias, exudative and constrictive pericarditis (COHN et coll 1967, TENERIELLO et coll 1970, GREENWOOD et coll 1974) myocardial fibrosis, abnormalities of the coronary arteries (TRACY et coll 1974) have been reported ECG abnormalities have been described by WHITFIELD & KUNKLER (1957) as well as abnormalities observed in the light microscope (cf JONES & WEDGWOOD) and in the electron microscope (BURCH et coll 1968) However, the opinions differ regarding the frequency and severity of the injury to the heart caused by radiation therapy of tumours in its neighbourhood (VAETH et coll 1961) as well as the pathogenesis behind the changes observed Irradiation may produce tissue injury directly or secondarily to vascular in [illegible]

[illegible]

[illegible] connection with irradiation for a variety of malig nant tumours The incidence and type of complaints and ECG abnormalities have

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When the ECG was recorded at rest only, the tracing covered 30 to 40 seconds When also an exercise test was performed the ECG was recorded continuously during and for at least 4 min after the exercise During exercise chest-head leads were recorded (HOLMGREN & STRANDELL 1961) All ECG abnormalities were classified according to the Minnesota code (BLACKBURN et coll 1960) as modified for use with CR leads and exercise testing (ÅSTRAND et coll 1967) ECG at rest was recorded before the treatment started, at the end of each week and at one and 6 months following termination of treatment Exercise ECG was recorded before the treatment started and one and 6 months after the end of treatment

Exercise tests were performed on an electrically braked bicycle ergometer with multiple submaximal 6-min loads increased in a stepwise manner (SJÖSTRAND 1960) The test was interrupted when the patient reached a heart rate of 170 beats per min or earlier if the patient had to stop because of general fatigue or other subjective complaints Using the linear relation between heart rate and load during exercise, the physical working capacity was determined or calculated by extrapolation as the load the patient could perform in a relatively steady-state at a heart rate of 170 beats per min (PWC_{170}) The reproducibility of PWC_{170} expressed as the standard error of a single determination is 4 9 per cent (HELLSTRÖM & HOLMGREN 1966) Exercise tests were carried out before the treatment period and one month and 6 months after the end of treatment

The heart volume was determined in the prone position according to LARSSON & KJELLBERG (1948) with a slight modification introduced by KJELLBERG et coll (1951) The reproducibility expressed as the standard error of a single determination is 4 2 per cent The heart volume was determined in those subjects who performed exercise tests and on the same occasions

Arterial blood pressure and heart rate after 10 min rest supine and after 8 min standing were recorded under standardized conditions The blood pressure was determined with a mercury manometer and the heart rate palpatorily for 30 s All the measurements were made in the same room, with the same manometer, on the same arm and by the same nurse To reduce psychologic influences the initial values were not recorded on the day diagnosis or treatment was announced to the patient, neither [illegible] ressure and heart rate were [illegible] each week during treatment [illegible] months after the end of treatment

Statistical calculations For each patient the difference between the first blood pressure control (week 0) and the one at the end of the first week of treatment (week 1) was tested for statistical significance separately, in order to avoid the influence of a possibly too high initial blood pressure on the evaluation of the blood pressure changes

Table 1

Patient material and radiation treatment given

Irradiated region	No of patients	Additional treatments during follow-up period*	Total absorbed dose (Gy)	Treatment period (days)
Head, neck, supraclavicular fossa, axilla	5	4	24–50	15–54
Mediastinum	36	11	12–58	16–84
Mantle technique	(27)	11	21 7–46	33–84
Other technique	(9)		12–58	16–55
Abdomen	12	2	12–44	17–63
Inverted Y-field	(10)	2	28–44	32–63
Other technique	(2)		12–43	17–53
Groin	2		24–35	20–35
Total	55			

* The same regions irradiated as in the first column

been recorded as well as blood pressure changes Their functional importance was evaluated by exercise tests before and after the treatment The results in patients with malignant lymphomas are now reported

Material

The material consisted of 55 patients (30 males and 25 females) irradiated for malignant lymphoma during the years 1969 to 1971 For technical reasons it was not possible to use all types of tests in each patient, in 4 patients only blood pressure and heart rate were recorded

The irradiated region and the distribution of the patients are given in Table 1, together with the absorbed tumour doses and the total period of treatment Additional irradiation was given in some cases during the follow-up period The patients were treated either with a ^{60}Co therapy unit or with roentgen radiation from a 6 MV linear accelerator In general the patients were irradiated five days a week with a daily tumour dose of 2 Gy (200 rad) The mediastinum was irradiated with the mantle technique in 27 of 36 patients In 10 of 12 patients with abdominal irradiation the inverted Y-field technique was used

Methods

ECG was recorded with a Mingograf 61 or 81 (Siemens-Elema, Solna, Sweden) Conventional 12-lead ECG was recorded, with the precordial leads as CR leads

Table 3

Physical working capacity (PWC_{130}, kpm/min, mean ± SEM) before and after treatment

	Before treatment	1 month after treatment	6 months after treatment
Male	1 004 ± 70 n = 13	931 ± 81 n = 10	1 009 ± 65 n = 11
Female	595 ± 30 n = 15	546 ± 29 n = 14	562 ± 31 n = 15
Mean of difference (d̄)		− 61*	+ 10
Probability (p)		< 0 01	n s
No of patients (n)		23	25

* Mantle and mediastinum group d̄ = − 76, p < 0 01, n = 17
Other regions d̄ = 17, p n s, n = 6

Table 4

Heart volume (ml, mean ± SEM) before and after treatment

	Before treatment	1 month after treatment	6 months after treatment
Male	799 ± 33 n = 13	774 ± 36 n = 12	804 ± 38 n = 11
Female	657 ± 37 n = 17	625 ± 39 n = 15	632 ± 35 n = 16
Mean of difference (d̄)		− 22	+ 6
Probability (p)		< 0 05	n.s
No of patients (n)		27	27

Results

ECG at rest was recorded in 51 subjects before the treatment started Abnormalities were noted in 15 of the patients (29 per cent, Table 2) ST depressions, with or without low or inverted T wave, corresponding to the left ventricle were observed in 6 subjects (Modified Minnesota code No 4 1–4 3, 4 5, 4 7) and isolated T wave changes in another 3 patients (code No 5 1–5 4) Definite evidence of an old myocardial infarction was noted in one patient and minor QRS abnormalities which possibly indicated minor myocardial infarctions were observed in 2 patients (code No 1 2 8, 1 3 2 1 3 4) During the treatment period ECG recording was repeated once a week in 34 of the patients During this period the frequency of atrial arrhythmia and of T wave changes slightly increased The latter appeared on an average after 4 weeks of treatment On the other hand, ST depressions were noted less frequently In total, ECG abnormalities were encountered in 19 of the 34 patients (56 per cent) At one and 6 months following treatment the frequency of arrhythmias, ST depressions and T wave changes were essentially the same as before treatment

Atrial arrhythmia or ventricular ectopic beats were observed in some patients during or after exercise only (code No 8 9, 10 6–10 8 and 10 2, 10 5, respectively) The

Table 2

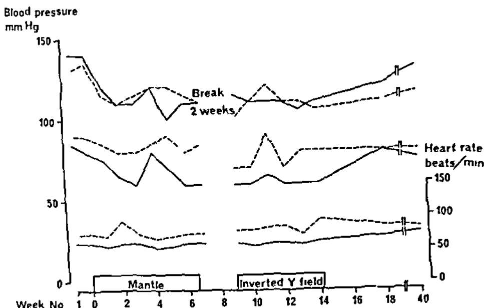
ECG abnormalities before, during and after treatment

ECG abnormality	Before treatment		During treatment	1 month after treatment		6 months after treatment	
	Rest	During or after exercise only	Rest	Rest	During or after exercise only	Rest	During or after exercise only
Atrial arrhythmias	1	4	4	1	1	4	1
Ventricular ectopic beats	1	3	1		4	1	
ST depression, alone or combined with T wave changes in left ventricular leads	6		2	3		2	
T wave changes	3		7	4		4	
QRS abnormalities	3		2	2		2	
Intraventricular conduction abnormalities	2		2	2		2	
Miscellaneous minor abnormalities	4		2	4		3	
No of patients examined	51		34	41		36	
No of patients with ECG abnormalities	15		19	13		12	
Fraction of patients with ECG abnormalities (per cent)	29		56	32		33	

during the rest of the treatment To eliminate the effects of individually differing blood pressure levels and of missing values among the patients, the change during the rest of the treatment periods was calculated by trend analysis The regression lines for systolic and diastolic blood pressure and for heart rate during the treatment period were calculated for each patient individually The t-test was applied in the determination of the statistical significance of the mean values of the regression coefficients for the whole group

Regarding physical working capacity and heart volume the statistical significance of the difference between the first and the second and third examination, respectively, has been calculated as paired differences and the t-test applied

Symptoms At the department of radiation therapy the patient was examined by the physician supervising the treatment, and a history was taken with particular reference to previous complaints referring to the cardiovascular system During the period of treatment the patient was examined and questioned about complaints once a week Almost all patients were under the care of the same physician



Blood pressure and heart rate supine (——) and standing (----) in a 34 year-old female with Hodgkin's disease treated with mantle technique and inverted Y fields for malignant lymphoma

mination one month following treatment, the average physical working capacity of the whole group had decreased slightly but statistically significantly This decrease occurred also in patients who were irradiated to the mediastinum but not in those with other regions irradiated (Table 3) No relation existed between reduction in physical working capacity and ECG abnormalities, change in blood pressure or age of the patient At the examination 6 months following treatment the physical working capacity had returned to pretreatment level in all groups

Heart volume The average heart volume was normal before treatment (Table 4) The individual values were within the normal range in all cases except two, who had heart volumes of 508 and 534 ml/m², respectively One month following treatment a slight reduction was found which was probably statistically significant both in the whole group and in the subgroup irradiated for mediastinal tumour Six months following treatment the heart volume had returned to pretreatment level In one patient the heart volume increased 125 ml while a decrease of 105 ml was found in another patient Otherwise all changes were less than 100 ml

Arterial blood pressure The mean value of the blood pressure at rest supine and standing was normal before treatment During the irradiation period a slight continuous decrease in blood pressure was found both in the supine and standing posi-

Table 5

Blood pressure and heart rate ($\bar{X} \pm SD$)

	Blood pressure (mm Hg)		Heart rate (beats/min)	No of patients
	Systolic	Diastolic		
Supine				
Week 0	129±15	76±12	81±13	36
» 1	123±13	71± 9	80±13	30
» 2	120±13	71±11	77±14	32
» 3	121±14	72±12	78±13	36
» 4	120±13	72±11	76±14	26
» 5	120±13	72±10	80±16	30
» 6	118± 9	70±10	82±15	21
1 month after treatment	121±11	74± 9	80±14	20
6 months after treatment	123±17	80± 9	80±14	11
Standing				
Week 0	126±17	85±11	95±16	33
» 1	117±14	83±10	96±12	27
» 2	119±13	83±10	93+16	30
» 3	120±14	83±12	93+14	33
» 4	120±13	85±11	91±13	24
» 5	118±13	84±11	95±16	27
» 6	119±12	84± 9	92+12	18
1 month after treatment	120±10	87+ 9	99±15	23
6 months after treatment	124+16	86±10	96±21	11

frequency of such arrhythmias was unchanged or had decreased one and 6 months following treatment

Intraventricular conduction abnormalities were observed in 2 patients (code No 7 2, 7 5) and miscellaneous minor abnormalities in 4 (code No 2 3, 8 7, 8 8, 9 3)

Appearance of ECG changes during or after treatment was almost the same in patients where the mediastinum had been irradiated compared to patients where other regions had been treated (12/34 and 5/17, respectively) No relation was found between the patient's age or the findings in the first ECG and the subsequent appearance of ECG changes

Physical working capacity Exercise test was performed in 34 patients The mean value of the physical working capacity was normal before the treatment in the 28 patients where PWC_{170} could be calculated (Table 3) The remaining 6 patients discontinued the test because of general fatigue, breathlessness or fatigue in the legs before enough data had been collected to calculate PWC_{170} Three of these patients had an ordinary heart rate in relation to the load while 3 had a high heart rate in relation to the load indicating a low physical working capacity At the first reexa-

Table 6 (*cont*)

End of treatment to 1 month after treatment			End of treatment to 6 months after treatment		
Mean difference	No of patients	Probability	Mean difference	No of patients	Probability
+5	20	<0 05	+2	11	n s
+2		n s	+7		<0 05
+4		<0 05	+2		n s
+4	20	<0 05	+7	11	n s
+3		n s	+4		n s
+3		n s	+1		n s

first treatment period the disease had progressed Splenectomy was performed and chemotherapy instituted The symptoms were essentially unchanged On physical examination the general condition was good and [illegible] pressure was 12 [illegible] at the second e[illegible] unchanged (39[illegible] respectively)

Discussion

The present material consisted of about 25 per cent of all patients treated for malignant lymphoma during the years 1969 to 1971 It represents a random selection as the capacity to handle the examinations and tests was the only factor that influenced whether a patient was included in the material or not

The incidence of ECG changes before treatment in this group is comparable to what has been found in health surveys in large groups of the general population of comparable age (FRISK et coll 1957) The increased frequency of arrhythmias found during treatment could possibly be explained by the fact that each patient was examined several times and hence the chance to find occasional ectopic beats increased However, this factor cannot explain the increased frequency of T wave changes observed during treatment The increased frequency of ectopic beats and of T wave changes was not related to the irradiation of the heart, as it appeared both in patients irradiated for thoracic tumours and in those with tumours in other parts of the body The disappearance after treatment is in accordance with the experience of HARTWEG and of WHITFIELD & KUNKLER

Table 6

Statistical significance of the changes in blood pressure and heart rate

	Week 0 to week 1			Week 1 to end of treatment		
	Mean difference	No of patients	Probability	Mean regression coefficient	No of patients	Probability
Supine						
Blood pressure						
Systolic	−4	30	<0 05	−1 52	36	<0 001
Diastolic	−4		<0 05	−0 64		<0 05
Heart rate	−2		n s	−0 00		n s
Standing						
Blood pressure						
Systolic	−6	28	<0 001	−1 13	34	<0 05
Diastolic	−1		n s	−0 23		n s
Heart rate	0		n s	0 16		n s

tions, but the heart rate was essentially unchanged (Table 5) Statistically significant reduction in both systolic and diastolic blood pressure supine and in systolic blood pressure standing occurred during the treatment period (Table 6) The initial values were partially restituted after the treatment period No relation was found between reduction in blood pressure and ECG abnormalities, change in physical working capacity or the anatomic region irradiated The decrease of the mean value was small, in about half of the patients the systolic blood pressure decreased with 0 to 10 mm Hg only and a similar decrease of the diastolic blood pressure occurred in about two thirds of the cases A considerable fall in blood pressure (more than 20 mm Hg systolic or diastolic) occurred in about one of 5 patients This may be illustrated by a case report (Figure)

Case report A 34-year-old woman with a malignant lymphoma and without previous cardiovascular symptoms She was treated according to the mantle technique and subsequently with an inverted Y-field technique During the latter part of the first treatment period she experienced vertigo on change of position, often with accompanying nausea The blood pressure fell from 140/80 to 100/70 during this period, but the heart rate was unchanged between 52 and 60 beats/min Physical examination of the heart revealed nothing abnormal ECG before treatment showed the cardiac rhythm to be initiated at rest by an ectopic atrial focus, while she had normal sinus rhythm during and after exercise The ectopic atrial rhythm persisted during the first and second week of irradiation and then disappeared Her physical working capacity (685 kpm/min) and heart volume (410 ml/m²) were normal During the second treatment period her fatigue and impaired general fitness persisted as well as vertigo and nausea, especially on change of position from supine The blood pressure stabilized around 105–110/60–65 mm Hg Six months after the end of the

während und 1 und 6 Monate nach der Behandlung bestimmt Es traten EKG-Abnormalitäten und ein Blutdrucksfall während der Behandlung auf. Eine herabgesetzte physische Arbeitskapazität wurde 1 Monat nach der Behandlung gefunden Nach 6 Monaten waren alle Parameter auf die Werte vor der Behandlung zurückgegangen Es sollte auf den wesentlichen Blutdrucksfall, der in einigen Fällen während der Behandlung auftritt, geachtet werden

RÉSUMÉ

Chez 55 malades irradiés pour lymphome malin, les auteurs ont étudié les signes fonc- [illegible]

constate une d[illegible] [illegible]

[illegible] cas au cours du traitement

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The physical working capacity was on an average normal in relation to what has been found in groups of the general population of comparable age and tested in the same way (FRISK et coll. 1957). The reduction in physical working capacity after treatment was generally slight, but it was more evident in patients irradiated for thoracic tumours indicating a more marked functional impairment.

The slight average reduction in heart volume found one month after treatment could be related to a decrease in or displacement of the blood volume as suggested by PITKÄ et coll. (1969). No clinical, radiographic or electrocardiographic evidence of pericardial effusion or myocardial insufficiency was encountered. However, the number of subjects is too small to permit any definite conclusion about the incidence of pericarditis in relation to what has been reported by COHN et coll. and up till now no long-term follow-up has been made.

During the treatment the blood pressure decreased slightly but statistically significantly at rest supine as well as in the standing position. In the majority of the patients the blood pressure changed very little but fell in some cases considerably, as reported previously by LEACH. The mechanism behind this is not clear, but is further discussed in another report (LARSSON et coll. 1976).

Except in 3 patients with ECG signs of myocardial infarction before beginning of the treatment, no ECG reactions or symptoms at rest or during exercise tests indicating ischaemic heart disease appeared in connection with the irradiation. Hence, the occurrence of angina pectoris or myocardial infarction reported after radiation therapy by TRACY et coll. was not confirmed.

In conclusion, slight transitory ECG abnormalities in connection with the radiation therapy and a slight, transitory, functional impairment of the cardiovascular system shortly after the treatment were found. Most important seems to be the marked fall in blood pressure appearing in some cases which may give the patient considerable discomfort. In patients on antihypertensive drugs it was found necessary to withdraw the drugs in a few cases and gradually resume the antihypertensive treatment as the blood pressure increased again after the end of the irradiation.

SUMMARY

In 55 patients irradiated for malignant lymphoma the complaints were recorded as well as ECG, blood pressure, exercise test and heart volume before, during and one and 6 months following treatment. ECG abnormalities and fall in blood pressure occurred during treatment. Reduced physical working capacity was found one month after treatment. After 6 months all parameters had returned to pretreatment levels. Attention should be paid to the considerable reduction in blood pressure that does occur in some cases during treatment.

ZUSAMMENFASSUNG

Bei 55 Patienten, die wegen eines malignen Lymphoms bestrahlt worden waren, wurden die Beschwerden, das EKG, der Blutdruck, der Arbeitstest und das Herzvolumen vor,

FROM THE GYNECOLOGIC SECTION, DEPARTMENT OF RADIATION THERAPY, UNIVERSITY HOSPITAL, S-221 85 LUND, SWEDEN

BLADDER AND INTESTINAL INJURIES FOLLOWING RADIATION THERAPY OF CARCINOMA OF THE UTERINE CERVIX

J E JOHNSSON

Curative treatment of malignant tumours always implies a risk of serious complications from organs in their immediate vicinity The bladder and the intestines are the organs most often affected by radiologic treatment of carcinoma of the cervix The literature discussing the types and frequency of complications is extensive (GRAY & KOTTMEIER 1957, FLETCHER et coll 1958, NOLAN 1962, HITTMAIR 1969, NIEMINEN et coll 1970, STROCKBINE et coll 1970, JOELSSON et coll 1971, BORONOW & RUTLEDGE 1971, WEGHAUPT 1971, VAN DER WALL 1971, KOB et coll 1972, MICKAL et coll 1972, ROSWIT et coll 1972, VILLASANTA 1972) The frequency of complications usually increases when a treatment technique is altered, and then slowly decreases as experience is gained (FLETCHER et coll , KOTTMEIER 1964)

The present report is an analysis of the types and frequency of complications arising in the bladder and intestines in connection with three different radiologic treatment techniques

Material and Methods The material consisted of invasive cervical carcinoma treated at different periods of time [illegible] stage of development have been [illegible] except that the border between [illegible] et coll (1963) and used since the beginning of 1969 Only those complications in the

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J E JOHNSSON

Curative treatment of malignant tumours always implies a risk of serious complications from organs in their immediate vicinity The bladder and the intestines are the organs most often affected by radiologic treatment of carcinoma of the cervix The literature discussing the types and frequency of complications is extensive (GRAY & KOTTMEIER 1957, FLETCHER et coll 1958, NOLAN 1962, HITTMAIR 1969, NIEMINEN et coll 1970, STROCKBINE et coll 1970, JOELSSON et coll 1971, BORONOW & RUTLEDGE 1971, WEGHAUPT 1971, VAN DER WALL 1971, KOB et coll 1972, MICKAL et coll 1972, ROSWIT et coll 1972, VILLASANTA 1972) The frequency of complications usually increases when a treatment technique is altered, and then slowly decreases as experience is gained (FLETCHER et coll , KOTTMEIER 1964)

The present report is an analysis of the types and frequency of complications arising in the bladder and intestines in connection with three different radiologic treatment techniques

Material and Methods The material consisted of invasive cervical carcinoma treated at different periods of time The criteria for classifying the material as regards the stage of development have been uniform throughout the material (KOTTMEIER 1964), except that the border between stages I A and I B was established according to FRICK et coll (1963) and used since the beginning of 1969 Only those complications in the

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urinary passages and the alimentary tract, caused by the primary treatment, and which required surgical measures, were recorded Those cases where malignant tissue was found in the walls of fistulas and perforational openings were not included Observation time was 2 years after completion of the radiologic treatment The number of patients still alive 2 years following initial treatment was recorded for the different groups in the material

Group I

This group consisted of 287 patients treated in the years 1952, 1953 and 1958 and were staged as follows Stage I A 7 patients (2 %), stage I B 56 (20 %), stage II A 53 (18 %), stage II B 98 (34 %), stage III 56 (20 %) and stage IV 17 patients (6 %) Two years after the initial treatment 205 patients (71 %) were still alive

Two intracavitary treatments were given at an interval of 3 weeks, using the *Stockholm technique The intrauterine and vaginal applicators were placed in the* uterus and vagina, respectively, without being fixed to each other The treatment time was standardized to 20 hours per session for both applicators (90 mg ^{226}Ra equivalent to 3 33 GBq in each applicator) No measurement of the dose in the bladder and rectum was performed

External treatment was also administered to two lower abdominal fields and to two lower dorsal fields, directed towards the parametria and the pelvic wall Irradiation parameters 180 kV, HVL 1 mm Cu, SSD 60 cm, field-size 200 cm^2 One field *treated each treatment day with an absorbed surface dose of approximately* 5 Gy (500 rad) to a total of 15–20 Gy (1 500–2 000 rad) on each field The abdominal fields were usually treated in connection with the first intracavitary treatment, and the dorsal fields at the time of the second treatment Extraperitoneal lymphadenectomy was performed 4 months after completion of irradiation in 133 (46 %) patients (GORTON 1953)

Group II

This group consisted of 116 patients treated in 1969 and were staged as follows Stage I A 20 patients (17 %), stage I B 38 (33 %), stage II A 19 (17 %), stage II B 20 (17 %), stage III 14 (12 %) and stage IV 5 patients (4 %) Two years after the initial treatment 87 patients (75 %) *were still alive*

External treatment was given to the contents of the true pelvis without any central shielding using ^{60}Co or 33 MV photons, depending on the thickness of the patient The absorbed dose varied with the extent of the tumour (*Stages I or II*), *33 Gy* (3 300 rad) ± 10 %, or 44 Gy (4 400 rad) ± 10 %, respectively, given in 17–18 fractions or 23–24 fractions, respectively Both of the opposing fields were treated daily five days a week In some cases, where only external treatment was given, four-field technique was used with an absorbed dose in the primary tumour of 62–65 Gy *(6 200–6 500 rad)*, split course, with a first series of 40 Gy, with 2 to 3 weeks intermission, and then 25 Gy

The intracavitary treatment was given using combined applicators (JOHNSSON & NORDBERG 1973) consisting of an intrauterine applicator (Ø7 mm × 68 mm 90 mg ^{226}Ra equivalent to 3 33 GBq), attached to a vaginal applicator (5 mm × 44 mm × 44 mm 110 mg ^{226}Ra equivalent to 4 07 GBq), which gives well-defined geometry for the dose of irradiation around the radium

The anatomic reference for the prescribed dose was Point A, defined as a point lying 2 cm laterally and 2 cm cranially from the point of contact between the intrauterine applicator and the centre of the vaginal applicator (approximately external os) The dose rate in Point A = 2 Gy/h (200 rad/h)

The absorbed dose in Point A on each treatment occasion was 25–35 Gy (2 500–3 500 rad) Measurement in the bladder and the rectum was performed with a Siemens gammameter The highest values measured were recorded The total dose in the bladder and the intestines from external and intracavitary treatment was not allowed to exceed 65 Gy (6 500 rad) Neither the different biologic effects of external and intracavitary treatment nor the effect of the fractionation was considered when calculating dose

Patients at the beginning of Stage I A received only two intracavitary treatments at an interval of 3 weeks Stages I and II were given primary external irradiation of the contents of the true pelvis followed by one intracavitary treatment 3 weeks after the completion of external treatment

External irradiation alone was given to cases in Stages III and IV, as well as to 18 patients in Stages I and II in whom the anatomy prevented the use of intracavitary treatment with radium

Group III

This group consisted of 271 patients, treated in the years 1970, 1971 and 1972 and were staged as follows Stage I A 39 patients (15 %), stage I B 78 (29 %), stage II A 77 (28 %), stage II B 33 (12 %), stage III 36 (13 %) and stage IV 8 patients (3 %) Two years after the initial treatment 198 patients (73 %) were still alive

External treatment was given in the same manner as in Group II, although external treatment alone up to full absorbed dose was not used Since 1972, mainly 8 MV photons from a linear accelerator were employed

Intracavitary treatment was given using combined applicators as for Group II, but for patients in whom the uterus was 8 cm or less in size, estimated with a sound, a shorter intrauterine applicator was used (Ø7 mm × 46 mm 60 mg ^{226}Ra, equivalent to 2 22 GBq) The vaginal applicator used had the same size as for Group II, but its contents were reduced to 90 mg ^{226}Ra, equivalent to 3 33 GBq Dose rate in Point A was 1 8 Gy/h (180 rad/h) Apart from this, the geometry of the dose distribution was the same as described

In those patients, in whom the size and form of the vagina were such that it was not possible to insert the combined applicators, only a rod-like applicator measuring Ø7 mm × 68 mm was used, which had a spacer of plexiglass (Ø25 mm × 25 mm) The

Table

Carcinoma of the uterine cervix stages I–IV Serious complications following radiation therapy Observation period Two years

	Group I (287 patients)	Group II (116 patients)	Group III (271 patients)
Bowel stenosis and necrosis	4 (1 5 %)	5 (4 %)	1 (0 5 %)
Recto vaginal fistulas	6 (2 %)	0	1 (0 5 %)
Vesico vaginal fistulas	4 (1 5 %)	0	0
Bladder necrosis	0	1 (1 %)	0
Total	14 (5 %)	6 (5 %)	2 (< 1 %)

applicator was placed in the cervix in such a way that 25 mm of its caudal part, which was capsuled in the centre of the plexiglass cylinder, lay in the upper part of the vagina Point A was defined in the same way as for the combined applicators The dose-rate in Point A was 1 6 Gy/h (160 rad/h)

The dose in Point A was 25–30 Gy (2 500–3 000 rad) for each treatment occasion The total dosage in the bladder and intestines from both external and intracavitary treatment was not allowed to exceed 62 Gy (6 200 rad)

Early cases in Stage I were only given two intracavitary treatments Stages I and II otherwise received the same external treatment as Group II, except that external treatment alone was not given up to full tumour dose Stages III and IV were given 55 Gy (5 500 rad) external irradiation to the primary tumour

All of the patients were given complementary treatment in the form of one intra cavitary irradiation, administered 3 weeks after completion of external treatment

Results

The complications recorded in the different patient groups included in the material appear in the Table

Group I Necrosis of the small bowel occurred in 2 of the 4 patients who had in testinal reactions Both of these patients expired as a result of these complications The others had a marked stenosis of the region between the sigmoid colon and the rectum No patient had more than one of the recorded complications during the period of observation

Group II One patient had necrosis of the small intestines This patient succumbed as a result of these complications The others had marked stenosis in the region be tween the rectum and the sigmoid colon Necrosis of the bladder was localized to the fundus of the urinary bladder and was accompanied by leakage of urine into the abdominal cavity It healed after surgical closure of the perforation No patient had more than one of the complications recorded during the period of observation

Group III One of the patients developed a perforation in the sigmoid rectum which opened into the abdominal cavity One patient had a recto-vaginal fistula No case of death due to complications was recorded in this group during the observation period

Discussion

Intracavitary treatment, which is the most common form of treatment used for cervical carcinoma, may cause complications first and foremost in the rectum and in the urinary bladder

The classic Stockholm method has been used for treating the primary tumour since the 1950 s Extraperitoneal lymphadenectomy (GORTON) has not implied any increase of complications in the bladder or the intestines The contribution to increased rates of complications from external treatment cannot be established with any degree of certainty, but ought to be rather small, if any

Fistulas between the bladder and the vagina, and between the rectum and the vagina, were dominant Their rate of occurrence was 1 5 and 2 %, respectively, i e close to the figures usually found in the literature

The technique used may have permitted uncontrolled doses of irradiation to have been given to the bladder and intestines, as the intrauterine and vaginal applicators were not fixed in an ideal position (JOHNSSON & NORDBERG 1973, FRIBERG & JOHNSSON 1974) No measurements of the dose-rate in the bladder and the rectum after application of the intracavitary preparation were made High dose-rates, which occur in these organs when the cervix is slender and thin even when correct applicator positions are used, therefore did not lead to the necessary reduction of the treatment time

Complications in the sigmoid colon and the small intestines are caused by the intrauterine applicator and arise when it extends far up in the uterine fundus, and especially when the uterine wall is thin The portions of the intestines lying in the true pelvis and mesenteric vessels may then receive quite high doses of irradiation (STROCKBINE et coll , FRIBERG & JOHNSSON)

Analysis of the treatment techniques and the curative results and complications obtained led to locking the intrauterine and vaginal applicators in a fixed treatment position, thus enabling a clearly defined radiation dose around them, and replacing external orthovoltage treatment and lymphadenectomy with external high-voltage irradiation Dose measurements were carried out in connection with the intracavitary treatments It was sometimes possible to adjust the position of the applicators in the true pelvis on the basis of these measurements When high dose-rates were nevertheless found the treatment time was reduced External irradiation was always given primarily and without central shielding External irradiation with central shielding following full tumour dose to the primary tumour from the intracavitary dose involves a risk of unpredictable underdosage to the cervix and parametrium or overdosage to the bladder and intestines (JOHNSSON & NORDBERG 1975) External ir-

radiation alone was given to all of the patients in Stages III and IV, and to those patients in whom it was not possible to apply satisfactorily the intracavitary applicators in the cervix and vagina

No recto-vaginal or vesico-vaginal fistulas were observed in this material This was probably due to locking the applicators to each other and also to the reduction of the intracavitary radiation treatment, which was replaced in part by external irradiation The rate of complications was, however, the same as in the previous material, although organs higher up in the true pelvis were affected Half of the recorded complications occurred in patients who had received only external irradiation The risk for complications when tumour dose in the true pelvis is administered solely by external irradiation has been reported by KOECK & HILLSINGER (1971), who reported 3 to 15 per cent serious complications using that technique CHAU et coll (1962) and MARUYAMA et coll (1974) have also reported an increase in complications in the intestines when the use of external high-voltage irradiation was increased Particularly in slender patients intestinal complications occur, as in such patients large parts of the intestinal tract often lie in the true pelvis

The size of the uterus is diminished by external irradiation, a size of 8 to 9 cm measured with probe before treatment is reduced to only 6 to 7 cm as a rule, 3 weeks after completion of treatment It is probable that the thickness of the uterine wall has been reduced correspondingly This implies that the same treatment time gives much higher doses outside the uterus than before the time of high-voltage irradiation Women having scanty fatty tissue between the uterus and the intestines and bladder receive higher doses of irradiation to these organs These factors probably contributed to necrosis of the bladder in one case and to colonic complications in 2 cases

A shorter intrauterine applicator has been used since 1970 and, in addition, external irradiation up to full tumour dose has not been given Patients with a narrow vagina have been given intracavitary treatment only using a rod-like applicator STROCKBINE et coll reported an increase of rectal complications from the use of such an applicator Use of a spacer in the present material, however, gave a well defined dose to the upper part of the vagina, and reduced the rectal dose to acceptable values No complications due to this applicator were found The intracavitary radiation dose was reduced by about 10 per cent in this material The recto-vaginal fistula developed in a patient who had received two intracavitary treatments with combined applicators Due to advanced multiple sclerosis her general condition was poor, she had ankylosed hip joints and reduced intestinal function The application was technically difficult, and the applicators were probably not placed correctly

The patient with a perforation of the sigmoid colon had been given external and intracavitary treatment The uterine fundus was apparently pressed against the sigmoid colon, resulting in high doses in that area No roentgen control of the position of the applicators was possible, the dose was measured in the rectum but not higher up in the colon

Fixation of the intrauterine and vaginal applicators to each other, so that they remain in a precise position during the treatment, yields a well-defined and reproducible radiation dose around them This implies that together with the measurement of the dose in the bladder and rectum, high doses of irradiation can be avoided or reduced Since introducing this technique, the frequency of recto-vaginal fistulas has been reduced from 2 to less than 0 5 per cent, and no vesico-vaginal fistulas have been recorded This is partly due to the reduction of the intracavitary radiation dose, which has been partially replaced with external high voltage irradiation

External high-voltage irradiation caused an increase of complications higher up in the true pelvis at the beginning, probably due to the fact that large parts of the intestine got high doses, and that the intrauterine applicators used were too long in a small uterus When these factors were considered, the complications in the colon and small intestines decreased from 4 to less than 0 5 per cent

A detailed analysis of the effects of the treatment techniques on the primary tumour and the regional lymph nodes must be available before a correct evaluation of the rate of complications can be made Such analyses will be presented in reports to be published in the future In the present report only figures on two-year survival are presented

Conclusion

The number of complications was reduced on the basis of the analysis made of different techniques of treatment The groups of patients are, however, from different periods of time and are not, therefore, strictly comparable Even though these results are not conclusive, the following statements can be made about the factors affecting the rate of complications

External high voltage irradiation giving full tumour dose to tumours in the true pelvis ought to be avoided, especially in thin patients However, doses around 40 Gy (4 000 rad) with 'usual' fractionation seldom appear to cause intestinal complications After initial external irradiation without shielding, the intrauterine applicator must be adjusted to the reduced length of the uterus (due to the effects of treatment), and it must not be allowed to extend up into the fundus The dose to the bladder and rectum should be measured in connection with the intracavitary applicators to permit correction of the dose

The intracavitary applicators ought to be designed in such a way as to give a well-defined and reproducible dose geometry when they are in position

SUMMARY

The frequency of serious complications in the bladder and intestines in 674 pat[illegible] radiated for carcinoma of the cer[illegible]
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mented with intracavitary treatment Difficulties in the Stockholm technique and in techniques combining external high-voltage and intracavitary treatment were taken into account, and the frequency of serious complications decreased to less than 1 %

ZUSAMMENFASSUNG

Die Häufigkeit ernster Komplikationen der Blase und des Darms bei 674 Patienten, die wegen eines Zervixkarzinoms unter Verwendung von drei verschiedenen Methoden behandelt worden waren wird, berichtet Die erste ist die Stockholm-Technik, die bei 5 % zu schweren Komplikationen fuhrte Bei den anderen zwei Methoden erhielten die Patienten primar eine externe Bestrahlung ohne eine zentrale Abschirmung, die durch eine intrakavitare Behandlung erganzt worden war Die Schwierigkeiten der Stockholm-Technik und der Methoden der mit der intrakavitaren Behandlung kombinierten externen Hochvolt-Therapie wurden berucksichtigt, wobei die Frequenz schwerer Komplikationen weniger als 1 % war

RÉSUMÉ

L'auteur présente la fréquence des complications vésicales et intestinales graves chez 674 malades irradiées pour cancer du col par 3 techniques différentes La première technique est la technique de Stockholm qui donne 5 % de complications graves Dans les deux autres techniques les malades recevaient en premier lieu une irradiation externe sans protection centrale, complétée par un traitement intracavitaire Les difficultés de la technique de Stockholm et des techniques qui associent un traitement externe de haute énergie et un traitement intracavitaire ont été prises en considération et la fréquence des complications graves s'est abaissée à moins de 1 %

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RADIATION SENSITIZING EFFECT OF DIAMIDE ON HUMAN CELLS CULTIVATED IN VITRO

E O PETTERSEN, R OFTEBRO and T BRUSTAD

Diazenedicarboxylic acid bis (N,N dimethylamide), diamide, oxidises intracellular non-protein SH (NPSH) specifically (KOSOWER et coll 1969) This finding led to the assumption that diamide might be a more efficient sensitizer of anoxic and extremely hypoxic cells to radiation than of aerobic cells (RÉVÉSZ et coll 1963, HARRIS et coll 1969)

This was found to be true for Pseudomonas fluorescence and for 3 Chinese hamster cell lines (V79, CHO and B14AF) cultured in vitro (HARRIS & POWER 1973) However, for a high concentration (200 μM) a low sensitizing effect was observed also for aerobic V79 cells The sensitizing effect by diamide on extremely hypoxic cells was reported by these authors to involve a reduction or removal of the shoulder of the dose survival curve *without* any effect upon the slope of the exponential portion of the curve This would give rise to a relatively efficient enhancement of radiation injury for low doses, in contrast to that found for the majority of other sensitizers, which commonly have little effect on the shoulder region, whereas the slope of the survival curve is increased for higher doses (PARKER et coll 1969, RÉVÉSZ & LITTBRAND 1970, ADAMS et coll 1971, CHAPMAN et coll 1971, 1972, PETTERSEN et coll 1973, 1974a) Therefore HARRIS & POWER suggested that enhanced cell damage by a given dose may be obtained by *combining* diamide with a slope-modifying sensitizer.

The ability of diamide to oxidise glutathione is reversed in the presence of glucose

Submitted for publication 4 December 1975

Book review

EARLY BREAST CANCER Its HISTORY AND RESULTS OF TREATMENT By C M Mansfield 129 pages, 32 tables and 366 references S Kargel, Basel 1976

The author of this book is a professor of radiation therapy and nuclear medicine at the Jefferson Medical College, Jefferson University Hospital, Philadelphia, Pennsylvania

The debate on the best treatment for breast cancer is emotionally biased Few objective investigations on such treatment have been carried out Most reports have been written in order to substantiate a point of view, to justify a certain method of treatment, or to condemn some other technique The book contains an exhaustive review of the treatment of breast cancer from ancient times and onwards, with the major section of the work devoted, of course, to the comprehensive literature from the past few decades The results of treatment with different surgical procedures, such as radical mastectomy, modified radical mastectomy, extended radical mastectomy, simple mastectomy, and local excision of nodules often combined with radiation therapy in various forms, are dealt with in comprehensive chapters The similarity between the results after different modes of treatment is striking

In recent years, extensive clinical randomized investigations regarding the treatment of breast cancer have been carried out The author points out that clinical investigations are impaired with considerable weakness, a completion has often proved difficult due to the fact that many physicians have shown little interest, or could only accept one or other of the therapeutic alternatives The book reviews the most important of the clinical reports but unfortunately the disadvantages of the various investigations are only briefly touched upon The clinical experiences have not in general demonstrated that any one method of treatment is better than others Up to the present, the only method that has shown a reduced recurrence rate is adjuvant chemotherapy, but the observation time is still too short to allow definite conclusions to be drawn

The conclusions reached by the author are that patients with operable breast cancer have the same chances for survival irrespective of whether they are treated by (1) Extended radical mastectomy (2) Radical mastectomy (3) Modified radical mastectomy, pre or postoperative irradiation reduces the local recurrence rate but probably does not increase the survival time (4) Simple mastectomy combined with irradiation (After the book was published the results of a randomized investigation started at King s College revealed that in stages I and II mastectomy alone seems to give the same result as mastectomy combined with irradiation) (5) Local excision of the tumour, with irradiation of the breast (6) Radiation therapy alone has not yet been tried in a sufficiently large number of cases in operable cancer The author therefore concludes that in general it is reasonable to offer the patient the form of treatment producing the least possible mutilation and giving the best cosmetic result

The author has succeeded in presenting an objective review of many subjective contributions to the debate on the treatment of breast cancer The title of the book Early Breast Cancer, may be misleading to some readers, in the manner of speaking often unfortunately employed this concept is approximately synonymous with operable The book gives a full review of the literature dealing with the treatment of breast cancer It may be recommended to all those who are interested in the management of this disease

Arne Wallgren

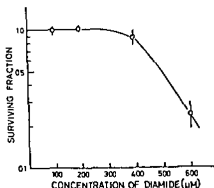


Fig 1

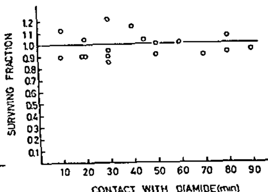


Fig 2

Fig 2 The effect of 200 μM of diamide on the reproductive capacity of NHIK 3025 cells in contact with diamide for different times under extremely hypoxic conditions The cells were kept under hypoxic conditions even during diamide addition

All irradiations were performed with 220 kV roentgen radiation The dose rate was 1 6-1 9 Gy/min (160–190 rad/min) for cells irradiated under extremely hypoxic conditions and 3 Gy/min for cells irradiated under aerobic conditions

Diamide was obtained from Calbiochem San Diego, California and used without further purification

Results

The surviving fraction versus diamide concentration for aerobic cells kept in contact with diamide for 2 hours at room temperature appears in Fig 1 The symbols represent the mean survival ratios based on 4 independent experiments and standard errors are indicated with bars The data show 200 μM to be the highest tested concentration without toxic effect under aerobic conditions

Diamide of a concentration of 200 μM is non toxic also for cells under extremely hypoxic conditions, for times of at least up to 90 min (Fig 2) Consequently, in the present experiments diamide was never used in concentrations exceeding 200 μM and the drug was never kept in contact with the cells for more than 90 min

The effect of diamide of concentration 200 μM on aerobically irradiated cells appears in Fig 3 Data from 2 different experiments are given In both experiments duplicate samples were irradiated, e g. in presence and absence of diamide No significant modifying effect of diamide under aerobic conditions was found

The dose-effect curve of extremely hypoxic NHIK 3025 cells irradiated suspended in E2a medium has been published previously (PETTERSEN et coll 1974b) Now 5

HARRIS et coll 1971, HARRIS & BIAGLOW 1972) HARRIS & POWER gave survival data only for cells irradiated in absence of glucose Thus, from a therapeutic point of view it would be of interest to investigate whether or not diamide acts as a sensitizer of hypoxic mammalian cells when glucose is present

HARRIS et coll (1974), using mouse tumours in vivo, found that the loss of non protein SH in vivo was only 25 per cent of that expected from in vitro data for a glucose-free medium The diamide concentration was approximately 1 7 mM within the tumour The reduced loss of non-protein SH in vivo was ascribed to the presence of glucose In spite of this finding a high dose modifying sensitizing effect was observed on hypoxic tumours while there was no effect on aerobic tumours This indicates that the concentration of NPSH may not be directly correlated with sensitivity to radiation, and therefore that the sensitizing effect of diamide may in some complicated way depend on the glucose concentration

The modifying effects of diamide (of various concentrations) on cells irradiated in growth medium, containing about 1 mg/ml glucose was experimentally investigated This glucose concentration is close to that of human blood The results are discussed in the light of the results presented by HARRIS & POWER and WATTS et coll (1975)

Materials and Methods

The experimental set up and techniques used for irradiation of aerobic and extremely hypoxic cells have been described previously (PETTERSEN et coll 1973) The irradiation was performed at room temperature with asynchronous populations of cells suspended in a mixture of growth medium E2a 75 %, and trypsin solution 25 % (PUCK et coll 1957)

Extremely hypoxic cells were obtained by a degassing procedure with a gas mixture of N_2 97 % and CO_2 3 % containing less than 4 ppm O_2 During degassing and irradiation (the degassing continued during irradiation) the cell suspension (max 20 ml) was kept in a Petri dish placed in a stainless steel chamber and was continuously agitated by a magnetic stirrer in the chamber A hypodermic needle mounted in the chamber wall (PETTERSEN et coll 1973) allowed samples to be extracted and diamide added without exposing the suspension to air

The toxic effect of diamide on reproduction of aerobic cells at room temperature was tested by exposing suspended cells to diamide at different concentrations for 2 hours The toxic effect of diamide on reproduction of extremely hypoxic cells was tested by adding diamide to a cell suspension deoxygenated by N_2 flushing for 15 min, then removing samples from the suspension for survival tests at different times after addition of the drug

Diamide was added to the suspensions of aerobic cells 10 to 20 min before irradiation and removed within 15 min after the termination of irradiation For cells irradiated under extremely hypoxic conditions diamide was added 45 to 60 min before the start of the irradiation and again removed within 15 min after the irradiation was completed Irradiation and sampling lasted about 20 to 30 min

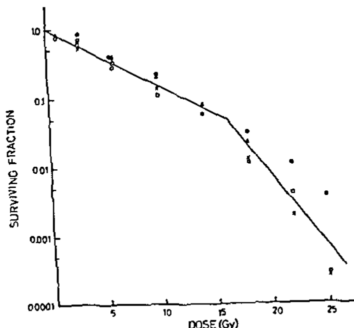


Fig 4 Dose-effect curve of extremely hypoxic (<4 ppm O_2) NHIK 3025 cells Five different and independent experiments are presented with one type of symbol for each. Exponential lines are drawn by hand

ceeds 400 μM However, it is difficult to draw further conclusions from this difference since HARRIS & POWER investigated the toxicity of diamide on cells kept in phosphate buffered saline at 4°C, whereas in the present experiments growth medium at room temperature was used Furthermore, the time of exposure to diamide was 15 min in the experiments of HARRIS & POWER and 2 hours in the present ones In spite of these differences the highest non toxic concentration on aerobic cells is for both groups found to be about 200 μM

WATTS et coll have exposed Chinese hamster cells to diamide for 2 hours while the cells were kept in growth medium (MEM + 15 per cent serum), or for 30 minutes while they were kept in Hanks' BBS In both cases they found a maximum non toxic concentration of diamide which was lower than 200 μM When the cells were kept in MEM + 15 per cent serum at 20°C the survival dropped to 75 per cent at 100 μM and to zero at about 300 to 400 μm indicating an even faster drop in survival than was found in the present experiments This suggests that the degree of toxicity of diamide is dependent on the cell system

The data in Fig 3 show that under the present experimental conditions no modifying effect of diamide on aerobic NHIK 3025 cells occurs This would be con

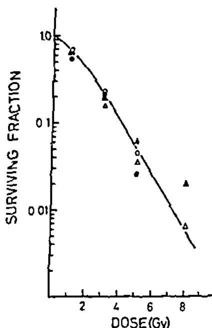


Fig 3 Dose-effect curve for aerobic NHIK 3025 cells irradiated in presence or absence of diamide at 200 μM Open symbols represent results for cells irradiated in absence, and closed symbols results for cells irradiated in presence of diamide Data from two independent experiments are presented, the one represented by triangels and the other by circles

independent experiments were performed to control the reproducibility of the previous results (Fig 4) Each type of symbol represents results from one single experiment The curve is drawn on basis of all points

The D_0 of the initial exponential line is 5 6 Gy and the D_0 of the exponential line at higher doses (above 18 Gy) is 2 3 Gy, which agrees well with the previous results

In Fig 5 data are presented from irradiation experiments with extremely hypoxic cells in contact with diamide of 3 different concentrations For comparison, the curve from Fig 4 is redrawn, but without the experimental points The vertical bars represent the standard errors of the experimental points in Fig 4

For diamide concentration of 20 μM no significant sensitizing effect occurred (Fig 5A) The low protective effect indicated at low doses is not considered significant This result agrees well with that found by HARRIS & POWER for Chinese hamster cells in presence of 20 μM of diamide and in absence of glucose

However, for a diamide concentration of 50 μM, the data indicate a low enhancement of radiation inactivation for doses above about 13 Gy (Fig 5B), for a diamide concentration of 200 μM a clear enhancement for doses above 8 Gy (Fig 5C) No modifying effect of diamide in the initial dose region (up to 8 Gy) was found for any concentration tested

Discussion

The toxic effect on NHIK 3025 cells (Fig 1) differs from that reported for different lines of Chinese hamster cells by HARRIS & POWER The survival of NHIK 3025 cells drops faster than that of Chinese hamster cells as the diamide concentration ex-

indicate that high concentrations of diamide may have a sensitizing effect on Chinese hamster cells under aerobic conditions The present results with NHIK 3025 cells irradiated under extremely hypoxic conditions in contact with 50 and 200 μM of diamide, also differ from those published by HARRIS & POWER They reported that diamide at 50 and 200 μM exerted a strong sensitizing effect at low doses The present data indicate no sensitizing effect at low doses On the other hand the present results confirm those of HARRIS & POWER in the sense that diamide does not exert any slope-modifying effect In their experiments high concentrations of diamide (50 or 200 μM) removed the whole shoulder of the hypoxic survival curve In the present experiments diamide concentrations of 50 and 200 μM reduced the initial exponential component of the hypoxic survival curve

WATTS et coll have published data for the sensitizing effect of diamide on hypoxic cells which have similar trends as the present ones Hypoxic cells in contact with 100 μM diamide in full medium exhibited no sensitization at low doses (<about 4 Gy) but a distinct sensitizing effect appeared at higher doses (i e a part of the shoulder had been removed in the presence of diamide) A comparison of the present experimental system with those of HARRIS & POWER and WATTS et coll suggests that the presence of glucose in the medium eliminates the sensitizing effect of diamide at low doses This suggestion is supported by the data of HARRIS et coll (1971) and HARRIS & BIAGLOW which indicate that the ability of diamide to oxidise glutathione is reversed in the presence of glucose

The results presented by HARRIS et coll (1974) on hypoxic P388 leucemia cells, grown in vivo as ascites tumours, indicated a dose-modifying sensitization by diamide In their experiments, the concentration of diamide in the tumours 1 min before irradiation was reported to be approximately 1 7 mM This concentration is almost 10 times higher than the highest one used in the present experiments Besides, since it is difficult to estimate the oxygen concentration in the hypoxic tumours, it is correspondingly difficult to compare the present data with the data presented by HARRIS et coll (1974)

Acknowledgements

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SUMMARY

Human cells of line NHIK 3025 were irradiated suspended in growth medium (E2a) in absence and presence of diamide under aerobic and extremely hypoxic ... tions A sensitizing effect of diamide was found for ... irradiated under extremely hypoxic conditions in ... 200 μM, whereas no significant effect was observed for 20 μM

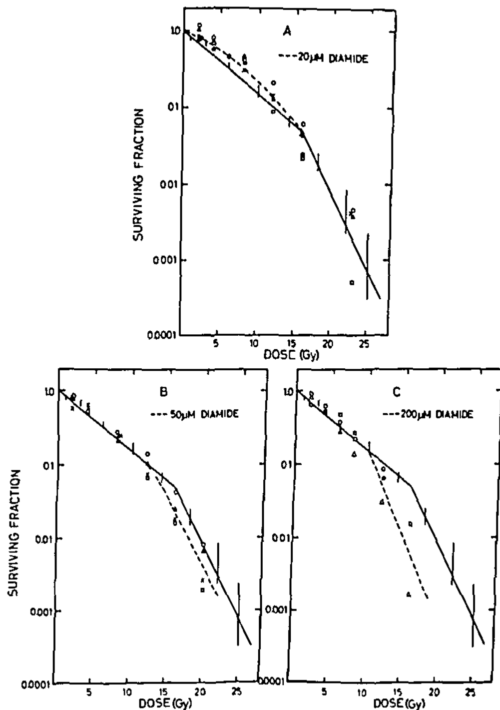


Fig 5 Dose-effect curves for extremely hypoxic NHIK 3025 cells irradiated in suspension in

PETTERSEN E O, OFTEBRO R and BRUSTAD T X-ray inactivation of human cells in tissue culture under aerobic and extremely hypoxic conditions in the presence and absence of TMPN Int J Radiat Biol 24 (1973), 285

— — — (a) Survival after X irradiation of extremely hypoxic human cells cultured in vitro Int J Radiat Biol 26 (1974), 305

— — — (b) The radiosensitizing and radioprotective effect of the organic nitroxyl free radical TMPN on extremely hypoxic human cells of line NHIK 3025, cultivated in vitro Int J Radiat Biol 26 (1974), 523

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ZUSAMMENFASSUNG

Humane Zellen der Linie NHIK 3025 wurden in einem Wachstumsmedium (E2a) suspendiert und mit und ohne Diamid unter aeroben und extremen hypoxischen (<4 ppm O_2) Bedingungen bestrahlt Ein sensibilisierender Effekt von Diamid wurde fur Dosen von mehr als 8 Gy (800 rad) bei Zellen unter extrem hypoxischen Bedingungen in Gegenwart von Diamid in einer Konzentration von 200 μM gefunden, wahrend kein signifikanter Effekt fur 20 μM zu beobachten war

RÉSUMÉ

Des cellules humaines de la lignée NHIK 3025 ont été irradiées en suspension dans le milieu de culture (E2a) en l'absence et en la présence de diamide dans des conditions aérobies et dans des conditions extrêmement hypoxiques (<4 ppm O_2) Les auteurs ont constaté un effet sensibilisant du diamide pour des doses dépassant 8 Gy (800 rad) sur des cellules irradiées dans des conditions extremement hypoxiques en présence de diamide à la concentration de 200 μM, alors qu'il n'y a pas d'effet observable important pour 20 μM

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Book review

PROPHYLAXE UND THERAPIE VON BEHANDLUNGSFOLGEN BEI KARZINOMEN DER FRAU Edited by Dietrich Schmahl Klinisch Onkologisches Seminar, Band 1 170 pages with 60 figures and 66 tables Georg Thieme Verlag, Stuttgart 1976 Price DM 44 —

The book contains a collection of lectures and discussions given at the recovery clinic Bad Trissl in Oberaudorf in 1975 A review is given of the radiation reactions, which may occur after treatment of malignant tumours in the gynaecologic organs and of the breast As a background, a general review of the effect of radiation in relation to doses and time factors is given The histologic abnormalities caused by the radiation are discussed

The complications which may occur in the skin, subcutaneous tissue, vessels nerves pleural cavity and lungs following irradiation of mammary tumours are reviewed They are related to the dose and quality of the radiation

Following irradiation of carcinoma of the uterine cervix, complications may be encountered in the pelvic connective tissue, ureters bladder, rectum sigmoid and small intestines The complications from the neck of the femur, which occurred after orthovoltage therapy have disappeared with the introduction of the high voltage technique The abnormalities of the blood vessels after irradiation are discussed and illustrated by angiographic films The reviews are thorough and of high value The authors also discuss the possibility of decreasing and avoiding radiation reactions in the skin and if they occur, how to treat them

Special attention is paid to the healing disturbances after laparotomy in patients who have been given preoperative irradiation

A detailed review is given of the frequency of different radiation reactions after treatment of gynaecologic malignant diseases Following treatment of carcinoma of the uterine cervix radiation proctitis is said to occur in 30 6 per cent necrosis in the rectum in 5 2 per cent and recto vaginal fistulas in 1 7 per cent Colostomies were indicated in 1 6 per cent Intestinal stenosis occurred in 4 8 per cent and intestinal perforations in 0 4 per cent Necrosis in the bladder occurred in 3 6 per cent and teleangiectasis in the bladder in 4 1 per cent Vesico uretero vaginal fistulas were recorded in 0 8 per cent

The complications following combined surgical and radiologic treatment of carcinoma of the uterine cervix are discussed It is also emphasized that the frequency of complications from the urinary tract is much higher in cases which only have been operated upon than in those irradiated

The indications and side effects of hypophysectomy in metastazing carcinoma of the breast are discussed as well as endocrine tumour therapy of gynaecologic malignancies and the effect of chemotherapy on the immunologic defence system The side effects of chemotherapy in treatment of malignancies are reviewed in detail The value of autologous bone marrow transplantation in severe complications is emphasized A review is given of the different types of chemotherapeutic agents and their side effects as well as of the sensitivity of the different organs

The book is very comprehensive and has a great value to those interested in the treatment of gynaecologic malignant tumours

Olle Kjellgren

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